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Review article

Antibiotic resistance monitoring in wastewater in the Nordic countries: A systematic review

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ABSTRACT

The Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) have effectively kept lower antibiotic-resistant bacterial (ARB) pathogen rates than many other countries. However, in recent years, these five countries have encountered a rise in ARB cases and challenges in treating infections due to the growing prevalence of ARB pathogens. Wastewater-based surveillance (WBS) is a valuable supplement to clinical methods for ARB surveillance, but there is a lack of comprehensive understanding of WBS application for ARB in the Nordic countries. This review aims to compile the latest state-of-the-art developments in WBS for ARB monitoring in the Nordic countries and compare them with clinical surveillance practices. After reviewing 1480 papers from the primary search, 54 were found relevant, and 15 additional WBS-related papers were included. Among 69 studies analyzed, 42 dedicated clinical epidemiology, while 27 focused on wastewater monitoring. The PRISMA review of the literature revealed that Nordic countries focus on four major WBS objectives of ARB: assessing ARB in the human population, identifying ARB evading wastewater treatment, quantifying removal rates, and evaluating potential ARB evolution during the treatment process. In both clinical and wastewater contexts, the most studied targets were pathogens producing carbapenemase and extended-spectrum beta-lactamase (ESBL), primarily *Escherichia coli* and *Klebsiella* spp. However, vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) have received more attention in clinical epidemiology than in wastewater studies, probably due to their lower detection rates in wastewater. Clinical surveillance has mostly used culturing, antibiotic susceptibility testing, and genotyping, but WBS employed PCR-based and metagenomics alongside culture-based techniques. Imported cases resulting from international travel and hospitalization abroad appear to have frequently contributed to the rise in ARB pathogen cases in these countries. The many similarities between the Nordic countries (e.g., knowledge exchange practices, antibiotic usage patterns, and the current ARB landscape) could facilitate collaborative efforts in developing and implementing WBS for ARB in population-level screening.

1. Introduction

Antibiotics are an important part of modern medicine, extensively used for therapeutic and prophylactic purposes in human and veterinary health care and the treatment of infections. However, antimicrobial resistance (AMR) has become one of the most serious global public health concerns due to the development and spread of resistance mechanisms, where bacteria reduce their susceptibility to antibiotics and treatment thus becoming less effective, leading to increasing morbidity, mortality, prolonged hospital stays, and increased healthcare

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costs (Muray et al., 2022).

The Nordic countries (Denmark, Finland, Iceland, Norway, Sweden, and their autonomous regions) are known for successfully maintaining a low prevalence of antibiotic-resistant bacterial (ARB) pathogens (WHO-ECDC, 2022). However, in recent years, the Nordic countries have faced an increase in ARB rates, particularly carbapenemase- and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* (e.g., *Escherichia coli* and *Klebsiella* spp.), vancomycin-resistant *Enterococcus* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA), largely due to international travel, hospitalization abroad, and immigration from ARB hotspot regions (Elstrøm et al., 2019; Espenhain et al., 2018; Ferløv-Schwensen et al., 2017; Gladstone et al., 2021; Helgason et al., 2016; Ingefors et al., 2022; Kanerva et al., 2015; Møller et al., 2019; Nielsen et al., 2022; Pinholt et al., 2019; Räisänen et al., 2020; Southon et al., 2020). On top of this, the effect of ongoing global warming and multiple recurring pandemics (such as COVID-19) on the abundance of ARB pathogens in this region is unknown. Therefore, the prevalence of ARB in the Nordic region may not remain low in the future.

Surveillance (i.e., thorough and careful monitoring) of ARB increases knowledge about their dissemination, helps in taking timely and appropriate management actions, and helps physicians with the wise selection of antibiotics for treatment (WHO, 2015). Currently, the member countries of the European Union/European Economic Area (EU/EEA) report the ARB pathogen status determined from invasive isolates (blood and cerebrospinal fluid) to the European Antimicrobial Resistance Surveillance Network (EARS-Net) as a regulatory surveillance approach (WHO-ECDC, 2022). EARS-Net covers resistance to eight pathogens, namely *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Streptococcus pneumoniae*, *S. aureus*, *Enterococcus faecalis, and Enterococcus faecium* (WHO-ECDC, 2022). The Nordic countries, except for Norway, also engage in the Global Antimicrobial Resistance and Use Surveillance System (GLASS), a surveillance mechanism led by the World Health Organization (WHO) (Table 1). This program compiles global data on certain ARB pathogen targets collected from blood, urine, and stool samples, and urethral and cervical swabs (GLASS, 2022). The Nordic countries, except for Iceland, have established nationwide AMR surveillance systems: the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP, 2023), the Finnish Study Group for Antimicrobial Resistance (FiRe, 2023), the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM, 2023), and Swedish Antibiotic Sales and Resistance in Human Medicine (SWEDRESS, 2023). These currently existing surveillance approaches provide comprehensive information on the most clinically significant ARB pathogens annually reported.

Wastewater-based surveillance (WBS) has emerged as a complementary tool to the current AMR/ARB pathogen surveillance, mostly but not solely at the human population level (Aarestrup and Woolhouse, 2020; Huijbers et al., 2019; Tiwari et al., 2022a). ARB pathogens and their genetic markers are excreted from feces, urine, nasal mucus, skin, and sputum to the sewage system soon after the beginning of infections and during different stages of infections (e.g., symptomatic, asymptomatic, pre-symptomatic, post-symptomatic) (Aarestrup and Woolhouse, 2020; Tiwari et al., 2022a). WBS is independent of the healthcare-seeking behavior of people and their access to healthcare facilities and tests (Diemert and Yan, 2019; Flach et al., 2021). Thus, WBS provides spatiotemporal information on the general prevalence of ARB pathogens, and, in principle, has the potential to provide information on the circulation of pathogens of all symptomatic and asymptomatic individuals in real time or even many days before the availability of clinical monitoring data (Blaak et al., 2021; Huijbers et al., 2019, 2020; Karkman et al., 2020; Pärnänen et al., 2019). As the WBS approach does not collect samples on an individual level, it has minimal legal and ethical challenges and individual privacy concerns (Auguet et al., 2021; Bowes et al., 2023). Because the cost of analysis of a wastewater sample for a pathogen is almost equivalent to the analysis of the pathogen in a clinical sample, WBS is a cost-effective approach for obtaining nearly real-time information about the circulation of a pathogen at the population level (Tiwari et al., 2023a). WBS also considers ARB profiles from the normal gut flora. This is crucial, because the development of antibiotic resistance is complex, with resistance genes frequently being transferred through horizontal gene transfer within mobile genetic elements (Carlet, 2012; Langdon et al., 2021).

The Nordic countries have employed WWS for monitoring ARB for many years (Flach et al., 2018, 2021; Grevskott et al., 2021; Heljanko et al., 2023; Huijbers et al., 2020; Hutinel et al., 2019; Jakobsen et al., 2008; Jørgensen et al., 2017; Khan et al., 2018, 2019; Kwak et al., 2015; Marathe et al., 2021; Paulshus et al., 2019a, 2019b; Radisic et al., 2023; Tiwari et al., 2022b, 2023b). However, there is currently a lack of a comprehensive understanding of the application of WBS for ARB in these countries. Here, we systematically reviewed the existing published peer-reviewed literature to provide an up-to-date overview of the status of monitoring for ARB pathogens in the Nordic countries through WBS. This study compiled existing knowledge regarding the WBS of ARB in these countries and identified potential discrepancies among these countries. It comprehensively compared the spatial trends of ARB in wastewater with current clinical surveillance studies to assess the extent to which wastewater monitoring parameters reflect clinically reported ARB and their associated genes. Additionally, this study has presented data on the prevalence of ARB in wastewater effluent and examines the associated public and environmental health concerns across the Nordic countries. The aspiration here is that this comparative analysis validates the usability of WBS in monitoring ARB and contribute to the advancement of WBS as a reliable source of information at the population level. Additionally, we anticipate that this study deepens our comprehension of the effectiveness of WBS and establish a standardized method for implementing WBS of ARB in the Nordic countries, given their commonalities and similarities (Fig. 1 and Table 1). A common regional strategy for WWS of ARB, like this, can serve as a successful example and inspiration for other regions worldwide.

2. Methodology

We followed the Preferred Reporting Items for Systematic Reviews

Table 1
Coordination and surveillance characteristics of ARB in Nordic countries, 2020 (WHO-ECDC, 2022).

Country	WHO AMR focal point appointed by the Ministry of Health/area agency	Multisectoral and One Health collaboration/ coordination	AMR action plan developed	National surveillance system for AMR in humans	Submits data to a regional network for AMR surveillance	Participates in a regional external quality assessment scheme	Enrolled in GLASS	Infection prevention and control in human health care	Optimizing antimicrobial use in human health
Denmark	Yes	Excellent	Yes	Excellent	Yes	Yes	Yes	Very Good	Very Good
Finland	Yes	Very Good	Yes	Very Good	Yes	Yes	Yes	Excellent	Very Good
Iceland	Yes	Excellent	Yes	Excellent	Yes	Yes	No	Good	Very Good
Norway	No	Excellent	Yes	Excellent	Yes	Yes	Yes	Excellent	Excellent
Sweden	Yes	Excellent	Yes	Excellent	Yes	Yes	Yes	Excellent	Excellent

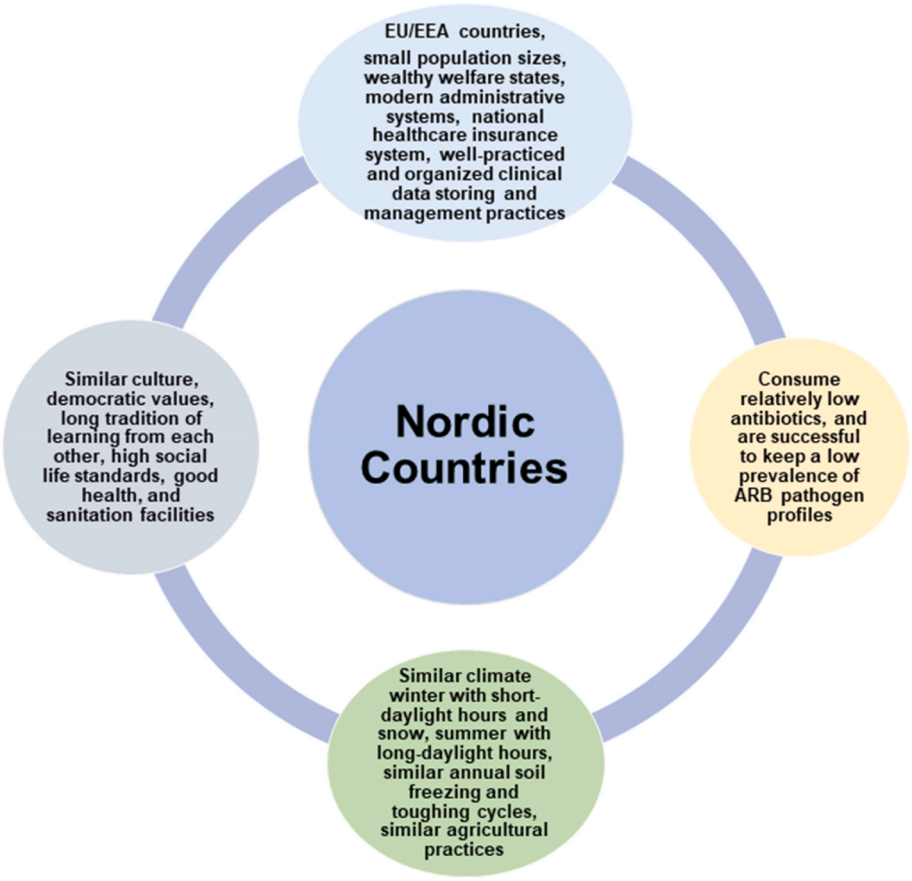


Fig. 1. Similarities and common values of the Nordic countries (Björkman et al., 2021; EC, 2020; Korhonen, 2018; Nordic cooperation, 2023; Time and Veggeland, 2020; Tiwari et al., 2021a).

and Meta-Analyses (PRISMA) guidelines for searching and reporting the literature review (Moher et al., 2009). Based on our study objectives, the systematic review sought literature related to human clinical epidemiology and (municipal and hospital) wastewater surveillance of ARB conducted in the Nordic countries. Three-stage screening strategies were applied to narrow down the search list at each stage, with (a) initial screening of the title, (b) careful reading of the abstract, and (c) thorough reading of the full paper (Fig. 2) (Moher et al., 2009).

A Boolean search technique was used in searching the literature by combining keywords with "AND" and "OR" in PubMed, Science Direct, Google Scholar, Web of Science, and Scopus, as in our earlier systematic reviews (Tiwari et al., 2022a, 2023a). Details of the search keywords are reported in Supplementary Material 1. Literature was retrieved from databases on a single day (January 22, 2023) with multiple search attempts. At first, all articles obtained from the primary search were saved in the reference management tool EndNote (Clarivite Analytics). Then, an automatic deduplication tool, "Find Duplicates," was used to remove duplicate publications obtained from various search engines. After this, the titles of the remaining papers were carefully screened to remove irrelevant and duplicate literature. In the next step, the abstracts of the remaining articles were carefully reviewed to find appropriate literature based on the research objectives. For clinical surveillance, studies collecting samples between 2010 and 2022 were considered. Regarding papers reporting wastewater monitoring for ARB, all available papers were considered and evaluated. The justification of the cutoff time point was two-fold: to evaluate the recent research trends and ARB burdens in the study area and, secondly, to gather enough research papers to enable comparison between the two types of data.

During the initial search, we included studies published in the English language without any restriction on the publication year. We excluded research that was not conducted in the Nordic countries, that was published in languages other than English, or that focused on veterinary or other zoonotic cases. We also excluded clinical case reports that described the treatment history or progress of a single patient, as well as technical reports, university theses, conference proceedings, and abstracts. Additionally, secondary literature (e.g., review papers and book chapters), letters to editors, and papers dealing with engineering, methodology, and modeling that did not report real epidemiological cases were also excluded. We further screened for additional relevant literature by reviewing the reference lists (based on screening of titles) of six previously published review papers with similar objectives (Aarestrup and Woolhouse, 2020; Chau et al., 2022; Karkman et al., 2018; Miłobedzka et al., 2022; Pruden et al., 2021; Tiwari et al., 2022a). Subsequently, we grouped the studies into two indistinct groups for further analysis: clinical surveillance and wastewater testing (Supplemental Data Sheet).

3. Results

3.1. Literature screening

A total of 1480 papers were initially retrieved from the primary database search (Fig. 2). After deduplication with an automated tool, a total of 533 papers remained. Subsequently, manual screening of the titles of these retrieved papers narrowed the selection to 452 papers. Further refinement involved excluding papers published before 2010 in clinical testing and those related to the animal and veterinary field, after which in a total of 194 papers remained. A thorough examination of the abstracts of these papers led to the selection of a total of 78 papers for a more comprehensive review. After a thorough reading of these papers,

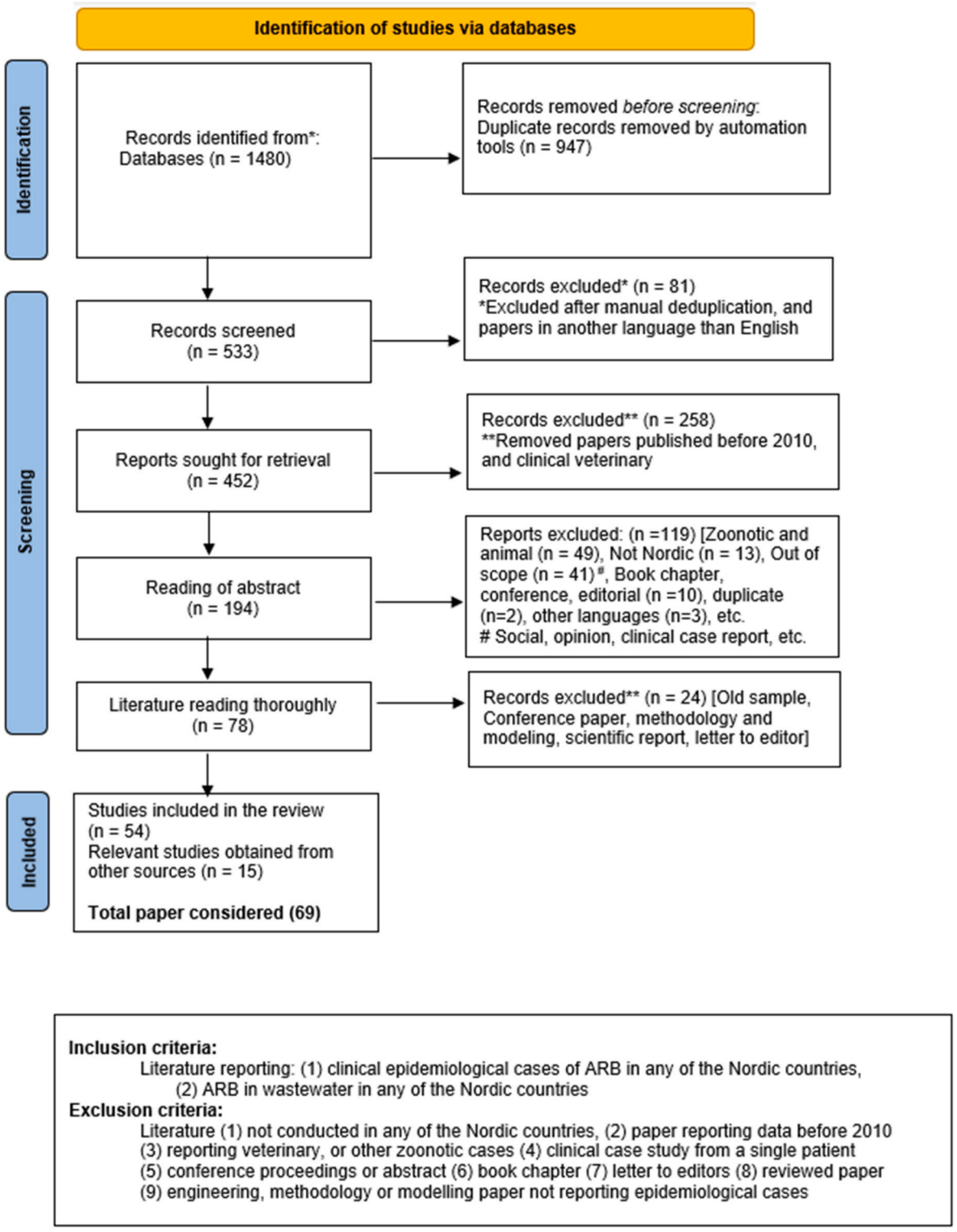


Fig. 2. Flow chart of the systematic review with inclusion and exclusion criteria for literature.

24 papers were subsequently excluded. The exclusions encompassed conference proceedings, methodology papers, engineering papers that introduced ARG or ARB into a simulated treatment processes to assess the reductions, book chapters, review papers, reports based on clinical samples collected before 2010, and papers published in languages other than English. As a result, 54 papers were retained for final consideration. Furthermore, an additional fifteen papers were considered: twelve papers retrieved from a reference search of published review papers (Aarestrup and Woolhouse, 2020; Chau et al., 2022; Karkman et al., 2018; Miłobedzka et al., 2022; Pruden et al., 2021; Tiwari et al., 2022a) and an additional three papers obtained based on expert recommendations. These publications were missed in the initial search due having broad titles that lacked the search keywords (Supplemental List 3). Regarding wastewater surveillance papers, we included all papers available in the database and a select few from additional sources to maintain a balance in the number of papers between clinical studies and

wastewater surveillance for comparisons. Herein, this study encompassed a total of 69 papers for final consideration, and out of these, 42 papers pertained to clinical reporting, while the remaining 27 papers reported on wastewater monitoring for the surveillance of ARB or ARGs.

Bacteria of the order *Enterobacterales*, including *E. coli*, *K. pneumoniae*, and *C. freundii*, were the main targets in both clinical and wastewater studies. For example, among clinical studies, a total of 23 out of 42 papers (54.8%) focused on infections caused by the *Enterobacterales* (Córdoba et al., 2017; Elstrøm et al., 2019; Fladberg et al., 2017; Gladstone et al., 2021; Hammerum et al., 2020; Hansen et al., 2020; Holmbom et al., 2020; Kanerva et al., 2012, 2015; Löfmark et al., 2015; Mehl et al., 2017; Österblad et al., 2012; Räisänen et al., 2020, 2021; Ramstad et al., 2021; Richelsen et al., 2020; Roer et al., 2017; Samuelsen et al., 2017, 2018; Sundvall et al., 2014; Thaulow et al., 2021; van Beek et al., 2019; Zykov et al., 2016). When considering the studies country-wise, in all the countries except Iceland, *Enterobacterales* was the most frequently targeted group in clinical testing (Table 2). Two species were solely targeted in clinical studies: *S. aureus* in nine studies (Di Ruscio et al., 2018; Edslev et al., 2018; Elstrøm et al., 2019; Eriksson et al., 2019; Fang et al., 2016; Holmbom et al., 2020; Kanerva et al., 2012; Møller et al., 2019; Nielsen et al., 2022) and *Enterococcus* spp. in seven studies (Elstrøm et al., 2019; Holmbom et al., 2020; Kaarme et al., 2015; Kanerva et al., 2012; Pinholt et al., 2017, 2019; Sundvall et al., 2014). Regarding wastewater monitoring studies, 17 out of 18 studies that utilized culture-based methods in wastewater monitoring targeted *Enterobacterales* groups (Flach et al., 2018, 2021; Grevskott et al., 2021; Heljanko et al., 2023; Huijbers et al., 2020; Hutinel et al., 2019; Iversen et al., 2002; Jakobsen et al., 2008; Khan et al., 2018, 2019; Kwak et al., 2015; Marathe et al., 2021; Paulshus et al., 2019a,b; Paulshus et al., 2019a,b; Radisic et al., 2023; Tiwari et al., 2022b, 2023b) (Fig. 3 and Supplemental Data Sheet S1). In wastewater monitoring, six studies monitored ARGs with qPCR or high-throughput qPCR (Cacace et al., 2019; Flach et al., 2021; Hutinel et al., 2022; Karkman et al., 2016; Laht et al., 2014; Majlander et al., 2021) and four studies targeted ARGs with metagenomics (Bengtsson-Palme et al., 2016; Brinch et al., 2020; Markkanen et al., 2023; Pärnänen et al., 2019).

Regarding clinical specimen types, 39% originated from blood/cerebral fluid, 14% from nasal swabs/upper respiratory tracts, and 10% from skin/soft tissue areas such as the eye and ear. It is worth noting that microbial loads to the wastewater system from these tissues can be relatively low compared to loads from stool and urine. The stool and urine samples collectively accounted for about 37% of the clinical specimens included in screening tests. Urine and catheter samples are typically collected when urinary tract infections (UTI) are suspected, and stool and rectal swab samples are taken when investigating the causes of gastrointestinal infections and for screening purposes (Kaarme et al., 2015; Löfmark et al., 2015; Österblad et al., 2012; Samuelsen et al., 2017). On the other hand, wastewater studies involved the collection of samples from various sampling locations, including influents and effluents of municipal wastewater treatment plants, raw sewage from hospitals, and recipient waters after the release of sewage effluent (Fig. 4). Currently, most of these studies represent academic research conducted over certain time frames and in specific locations. As a result, there is a noticeable absence of continuous, long-term data from wastewater monitoring in the existing literature.

3.2. Clinical studies on antibiotic-resistant bacteria in the Nordic countries

This literature review revealed variation in ARB pathogens between the Nordic countries, depending on the bacterial species and antibiotic classes (Table 3). Nevertheless, the variation was not as high as with many other EU/EEA countries (Tables S1 and S2) (WHO-ECDC, 2022). Among the Nordic countries, based on the percentage of invasive isolates with an ARB phenotype reported in EARS-Net (2016–2020), (a) Denmark had the highest percentage of vancomycin-resistant *E. faecium*, fluoroquinolone-resistant *Acinetobacter* spp., and carbapenem-resistant *K. pneumoniae*, (b) Finland had the highest percentage of fluoroquinolone-resistant *P. aeruginosa*, (c) Iceland had highest percentage of aminopenicillin-resistant *E. coli*, gentamicin-resistant *E. faecalis*, penicillin-resistant, and macrolide-resistant *S. pneumoniae*, (d) Norway had highest percentage of fluoroquinolone-resistant *K. pneumoniae*, and (e) Sweden had highest percentage of fluoroquinolone and aminoglycoside-resistant *E. coli* and carbapenem-resistant *P. aeruginosa* (see resistance rates in each country in Table 3). According to EARS-Net (2016–2020), when considering only *K. pneumoniae* and *E. coli*, third-generation cephalosporin resistance was generally higher in *E. coli* and carbapenemase resistance was higher in *K. pneumoniae* (see resistance rates in Table 3). Overall, carbapenem resistance was higher in *P. aeruginosa* and *Acinetobacter* spp. than in *K. pneumoniae,* and rare in *E. coli* due to their unique resistant mechanism. Furthermore, fluoroquinolone and aminoglycoside resistance was relatively higher in *E. coli* (Table 3).

a) Enterobacteriaceae

A total of 23 out of 41 clinical studies (54.8%) reported bacterial infections caused by *Enterobacterales*, mostly *E. coli, K. pneumoniae*, and

Table 2
Targeted ARB in clinical surveillance in the Nordic countries.

Country	Bacterial group			
	Enterobacterales	*S. aureus*	*Enterococcus* spp.	Others
Denmark	Six studies (Córdoba et al., 2017; Hammerum et al., 2020; Hansen et al., 2020; Richelsen et al., 2020; Roer et al., 2017; Samuelsen et al., 2018)	Three studies (Edslev et al., 2018; Møller et al., 2019; Nielsen et al., 2022)	Two studies (Pinholt et al., 2017, 2019)	One each targeted *Bacteroides fragilis* (Ferløv-Schwensen et al., 2017), *H. influenzae* (Fuursted et al., 2016), and *A. baumannii* (Hammerum et al., 2015)
Finland	Six studies (Kanerva et al., 2012, 2015; Österblad et al., 2012; Räisänen et al., 2020, 2021; van Beek et al., 2019)	One study (Kanerva et al., 2012)	One study (Kanerva et al., 2012)	One study *H. pylori* (Kostamo et al., 2011), one study *Pseudomonas aeruginosa*, and *Acinetobacter* spp. (Kanerva et al., 2012)
Iceland				*S. pneumoniae* (Hjálmarsdóttir et al., 2020) and *S. pyogenes* (Southon et al., 2020).
Norway	Eight studies (Elstrøm et al., 2019; Fladberg et al., 2017; Gladstone et al., 2021; Mehl et al., 2017; Ramstad et al., 2021; Samuelsen et al., 2017; Thaulow et al., 2021; Zykov et al., 2016)	Two studies (Di Ruscio et al., 2018; Elstrøm et al., 2019)	One study (Elstrøm et al., 2019)	One study *H. influenzae* (Tønnessen et al., 2022).
Sweden	Three studies together with multiple pathogens (Holmbom et al., 2020; Löfmark et al., 2015; Sundvall et al., 2014)	Three studies (Eriksson et al., 2019; Fang et al., 2016; Holmbom et al., 2020)	Two studies (Holmbom et al., 2020; Sundvall et al., 2014)	Two studies *Acinetobacter* species (Holmbom et al., 2020; Ingefors et al., 2022), *S. pneumoniae* (Holmbom et al., 2020) & one study *H. influenzae* (Tyrstrup et al., 2017)

Note: Elstrøm et al. (2019), Holmbom et al. (2020), Kanerva et al. (2012), and Sundvall et al. (2014) targeted multiple targets.

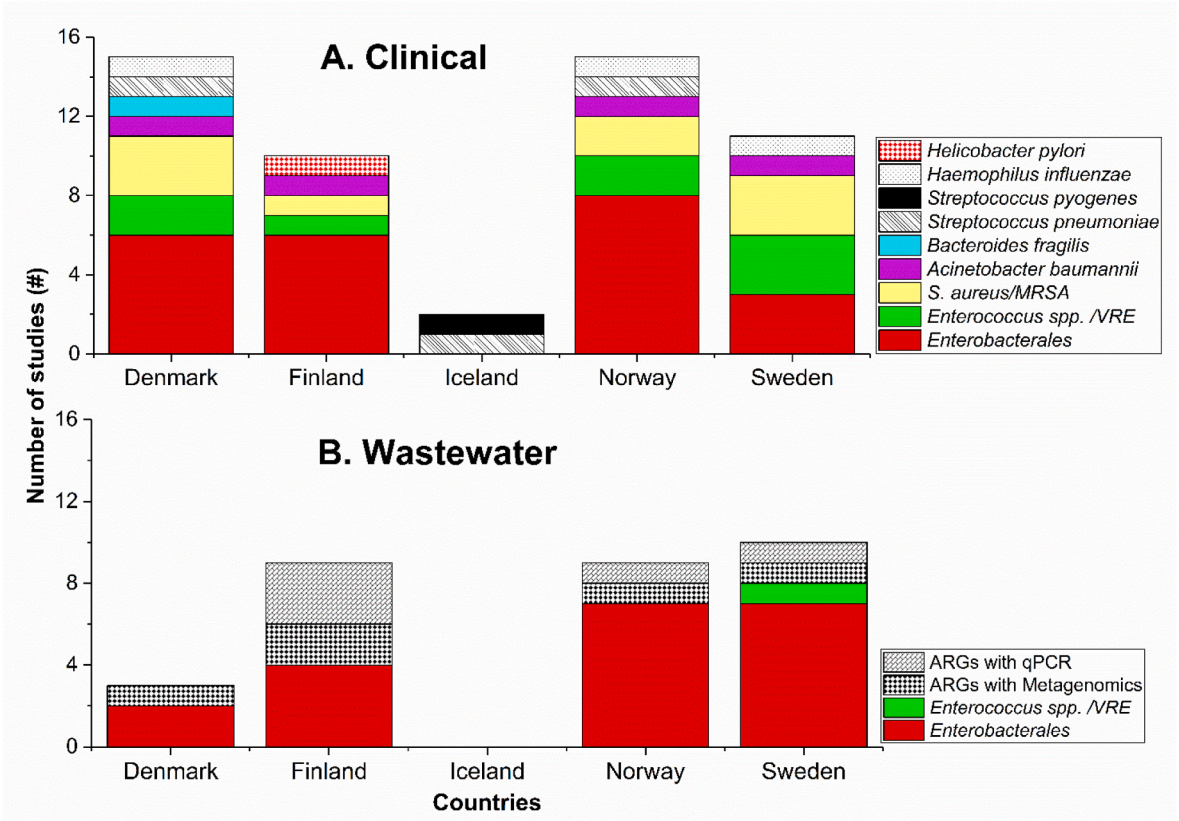


Fig. 3. Targets and microbes in reported ARB studies in the Nordic countries: A) Clinical surveillance and B) Wastewater testing.

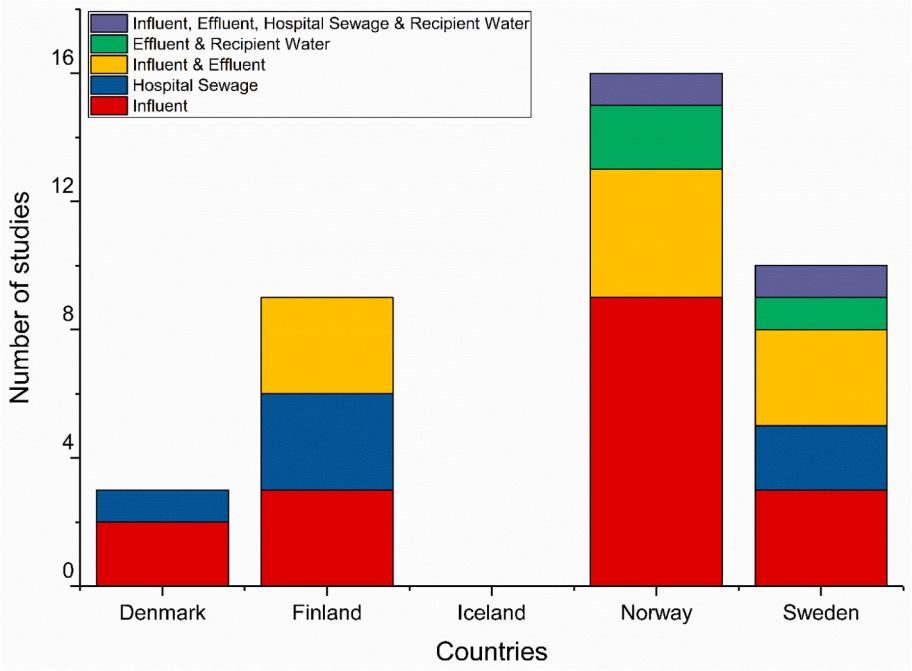


Fig. 4. Wastewater sample collection locations in reported studies in the Nordic countries.

C. freundii (Córdoba et al., 2017; Fang et al., 2016; Fladberg et al., 2017; Gladstone et al., 2021; Hammerum et al., 2020; Hansen et al., 2020; Holmbom et al., 2020; Kanerva et al., 2012, 2015; Löfmark et al., 2015; Mehl et al., 2017; Österblad et al., 2012; Räisänen et al., 2020, 2021; Ramstad et al., 2021; Richelsen et al., 2020; Roer et al., 2017; Samuelsen et al., 2017, 2018; Sundvall et al., 2014; Thaulow et al., 2021; van Beek et al., 2019; Zykov et al., 2016). Most of these studies targeted *E. coli* from bloodstream infections and UTIs.

In Denmark, a hospital outbreak of $bla_{\text{NDM-5}}$-producing *K. pneumoniae* was reported in 2014 (Hammerum et al., 2015).

Table 3
Percentage of isolates with an ARB phenotype (%) in the Nordic countries by bacterial species and antibiotic group/agent, population-weighted EU/EEA mean, 2016–2020 (WHO-ECDC, 2022).

Pathogen	Reporting year	Denmark					Finland					Iceland					Norway					Sweden				
		2016	2017	2018	2019	2020	2016	2017	2018	2019	2020	2016	2017	2018	2019	2020	2016	2017	2018	2019	2020	2016	2017	2018	2019	2020
	Antibiotics	Resistance percentage (%)																								
E. coli	**Aminopenicillin**	45.0	45.6	46.0	46.3	44.1	35.8	35.2	35.3	35.5	34.1	43.8	41.3	**49.0**	**52.5**	**55.1**	42.9	42.2	42.3	41.0	39.8	ND	ND	ND	ND	ND
	3RD G cephalosporins	6.6	6.9	7.7	7.5	6.7	6.9	6.9	7.6	7.8	7.2	4.2	6.1	8.1	7.0	**11.0**	5.6	5.9	6.8	6.2	5.8	**8.3**	7.4	**8.3**	7.8	7.9
	Carbapenem	0.0	0.0	0.0	0.1	0.2	0.0	0.0	0.0	0.0	0.0	NC	NC	0.0	NC	0.0	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
	Fluoroquinolone	11.0	12.8	13.3	11.5	11.2	11.5	12.0	11.4	11.4	10.5	9.6	11.6	**17.2**	13.1	11.8	10.9	13.6	12.9	11.3	10.0	13.7	15.8	**18.1**	**15.9**	14.1
	Aminoglycoside	6.1	6.0	5.7	5.5	5.5	4.9	5.0	4.3	4.8	5.7	3.6	5.6	6.1	4.7	**7.8**	5.5	**7.2**	5.7	5.6	5.7	**7.2**	6.5	**7.7**	6.0	5.9
K. pneumoniae	**3RD G cephalosporins**	7.5	7.3	6.5	6.7	6.0	4.1	4.6	4.5	6.3	7.2	0.0	5.9	0.0	4.3	0.0	5.8	5.8	7.5	7.7	**10.1**	4.9	5.6	5.5	**8.3**	**8.1**
	Carbapenem	0.3	0.3	**0.5**	0.3	**0.8**	0.3	0.3	**0.6**	0.4	0.1	NC	ND	NC	ND	0.0	0.0	0.0	0.1	0.2	0.1	0.1	0.1	0.2	0.1	0.3
	Fluoroquinolone	5.3	9.1	8.5	9.6	7.6	2.7	7.9	6.3	7.3	7.4	0.0	6.3	0.0	4.3	0.0	4.3	10.2	**13.1**	8.8	**11.2**	5.4	9.8	10.1	**10.5**	10.2
	Aminoglycoside	3.2	3.2	3.3	3.5	3.3	2.3	2.9	2.6	4.2	5.8	0.0	**11.8**	0.0	**8.7**	0.0	3.3	4.2	5.3	6.1	**7.3**	3.4	4.7	3.0	4.2	3.6
P. aeruginosa	**Carbapenem**	2.4	2.5	5.2	3.3	4.4	6.0	6.1	4.9	6.3	3.7	5.9	0.0	0.0	0.0	**12.0**	6.7	3.4	4.8	7.4	6.4	**11.0**	9.0	4.4	**9.8**	4.2
	Fluoroquinolone	3.7	5.0	4.3	5.5	3.2	7.9	**11.2**	**12.8**	8.5	10.2	**17.6**	11.8	8.3	4.5	4.0	5.7	4.9	10.4	5.7	8.5	6.0	9.0	7.1	9.2	7.4
	Aminoglycoside	1.7	1.0	0.6	**2.7**	0.0	**2.3**	1.9	1.0	0.7	1.4	0.0	0.0	0.0	**4.5**	0.0	0.9	0.5	0.8	0.3	0.4	0.8	0.9	1.0	**2.3**	0.6
***Acinetobacter* spp.**	**Carbapenem**	0.0	0.0	**6.4**	0.0	4.7	0.0	2.7	0.0	0.0	**5.4**	NC	NC	NC	NC	NC	0.0	0.0	0.0	0.0	0.0	1.2	0.0	3.7	3.6	**7.1**
	Fluoroquinolone	2.8	1.5	**9.1**	6.9	**13.8**	0.0	2.7	0.0	0.0	**8.3**	NC	NC	NC	NC	NC	3.0	0.0	0.0	0.0	0.0	4.7	0.0	7.3	8.0	7.1
	Aminoglycoside	0.0	0.0	**7.5**	2.8	4.6	3.6	0.0	**7.4**	0.0	2.7	NC	NC	NC	NC	NC	3.1	0.0	0.0	4.3	0.0	5.9	0.0	5.5	5.3	**8.0**
S. aureus	**MRSA**	2.0	**2.5**	1.7	2.2	1.7	2.2	2.0	2.0	2.1	**2.5**	1.3	1.4	0.0	**6.6**	5.2	1.2	1.0	0.9	1.1	1.7	2.3	1.2	1.9	1.8	2.3
S. pneumoniae	**Penicillin**	6.1	3.9	5.5	5.0	6.8	10.3	10.5	11.5	12.0	11.5	10.5	***18.5***	9.7	***15.9***	***30.0***	4.4	4.8	5.0	6.3	7.4	7.1	6.1	5.2	6.5	8.5
	Macrolide	4.8	3.6	2.5	3.5	3.7	11.4	15.0	12.1	10.5	11.8	0.0	***18.5***	12.9	***15.9***	***30.0***	5.3	5.5	7.6	5.7	5.1	5.3	4.7	4.5	6.5	6.6
E. faecalis	**High-level gentamicin**	**19.6**	7.1	12.3	8.5	11.8	ND	ND	ND	ND	ND	**16.7**	**18.2**	**16.7**	11.4	6.7	15.8	14.4	13.4	12.1	12.4	13.4	13.3	12.8	10.0	10.1
E. faecium	**Vancomycin**	7.5	7.0	**12.5**	**9.8**	**9.6**	0.0	0.7	1.7	0.0	0.4	0.0	0.0	0.0	0.0	0.0	1.9	4.5	2.3	1.0	0.6	0.4	0.0	1.4	1.0	0.2

Aminopenicillin = amoxicillin/ampicillin; Third-generation (3rd G) cephalosporin = cefotaxime/ceftriaxone/ceftazidime; Carbapenem = imipenem/meropenem; Fluoroquinolone = ciprofloxacin/levofloxacin/ofloxacin; Aminoglycoside = gentamicin/netilmicin/tobramycin; Macrolide = azithromycin/clarithromycin/erythromycin; ND = not available/not done; NC = Not calculated due to small sample size (<10); Bold numbers = Highest three percentage values of the row; values highlighted in bold and italicised are above the average EU/EEA values.

Subsequently, between 2014 and 2018, a total of 103 isolates were screened and bla_{OXA-48} and bla_{NDM-1} were reported as the predominant carbapenemase types found in *K. pneumoniae* (Hammerum et al., 2020). Additionally, Hansen et al. conducted a study in Denmark in 2018 focusing on *K. pneumoniae* isolates in invasive specimens. They reported the most common gene types to be $bla_{CTX-M-15}$ for ESBL, bla_{DHA-1} for *Amp*C beta-lactamases, and bla_{OXA-48} for carbapenemase (Hansen et al., 2020). Roer et al. investigated a total of 552 third-generation cephalosporin-resistant *E. coli* isolates collected from bloodstream infections in Denmark between 2014 and 2015. Their findings revealed that $bla_{CTX-M-15}$ was the most prevalent type, at 50%, followed by $bla_{CTX-M-14}$ at 14%, $bla_{CTX-M-27}$ at 11%, and $bla_{CTX-M-101}$ at 5% (Roer et al., 2017).

In Finland, Österblad et al. analyzed isolates from 2008 to 2011 and reported 26 clinical isolates of carbapenemase-producing *Enterobacterales* (CPE) originating from 25 patients. Among these, *K. pneumoniae* accounted for 61.5%, *E. coli* for 23.1%, and *Enterobacter cloacae* for 11.5% of the cases (Österblad et al., 2012). A subsequent study by Räisänen et al. analyzed 231 CPE isolates collected during 2012–2018 from 202 patients. Among the isolates, 32% were from clinical infections and the rest were from screening specimens. The prevalent species carrying the carbapenemase gene in this study were *K. pneumoniae* (45%), *E. coli* (40%), and *C. freundii* (6%) (Räisänen et al., 2020). Interestingly, both Finnish studies highlighted a strong association between CPE cases and travel abroad or hospitalization abroad, with a prevalence of 72% in the initial study and 63% in the subsequent one (Österblad et al., 2012; Räisänen et al., 2020). Regarding the types of carbapenemase genes, Österblad et al. (2012) reported $bla_{OXA-48-like}$ genes (38.5%), followed by bla_{KPC} (19.5%), bla_{VIM} (15.4%), bla_{NDM} (11.5%), and $bla_{IMI/NMC-A}$ (11.5%) as the most common (Österblad et al., 2012). According to Räisänen et al. among 231 isolates, bla_{NDM} was the most prevalent (35%), closely followed by bla_{OXA-48} (33%) and bla_{KPC} (31%) (Räisänen et al., 2020). A later Finnish study targeting carbapenemase-producing *C. freundii* clusters during the years 2016–2020 reported 21 isolates from 20 clinical patients, with bla_{KPC-2} as the most dominant (80%) resistance gene (Räisänen et al., 2021).

Helgason et al. reported the first detection of carbapenemase-producing *E. coli* isolates in Iceland, found in a rectal swab screening specimen from a hospitalized child who originated from the Philippines (Helgason et al., 2016). This isolate was confirmed to carry bla_{NDM-1} gene (Helgason et al., 2016).

In a study conducted in Norway from 2012 to 2017, a total of 231 carbapenemase-producing isolates were identified, which were collected from 195 patients (Elstrøm et al., 2019). The majority of these cases (83%) were associated with a nosocomial origin, and a significant proportion (73%) had a history of travel abroad (Elstrøm et al., 2019). The predominant pathogens in this study were CPEs (59.3%), followed by *Acinetobacter* spp. (29.9%) and *Pseudomonas* spp. (10.8%) (Elstrøm et al., 2019).

In Sweden, a study including isolates from 2007 to 2013 reported a total of 94 CPE isolates, with 24 obtained from clinical specimens and the remainder from screening specimens. The primary pathogens carrying the carbapenemase gene in this study were *K. pneumoniae* (61%), *E. coli* (31%), and *E. cloacae* (5%). Among the various gene types, bla_{NDM} was the most prevalent (n = 36), followed by the bla_{OXA-48} group, bla_{KPC}, and bla_{VIM} (Löfmark et al., 2015). Notably, 81% of the CPE cases in this study had a history of travel or hospitalization abroad (Löfmark et al., 2015).

b) *Staphylococcus aureus*

A total of nine studies, including three from Denmark (Edslev et al., 2018; Møller et al., 2019; Nielsen et al., 2022), one from Finland (Kanerva et al., 2012), two from Norway (Di Ruscio et al., 2018; Elstrøm et al., 2019), and three from Sweden (Eriksson et al., 2019; Fang et al., 2016; Holmbom et al., 2020), have reported cases of resistance in *S. aureus* within clinical settings. Among these, three studies also reported methicillin-resistant *Staphylococcus aureus* (MRSA) cases while simultaneously monitoring other targets in bacteremia cases (Elstrøm et al., 2019; Holmbom et al., 2020; Kanerva et al., 2012). Four studies specifically targeted dermal infections (Edslev et al., 2018; Eriksson et al., 2019; Møller et al., 2019; Nielsen et al., 2022). Among these, one study reported multiple infection types, including skin abscesses, wound infections, screening swabs from the upper respiratory tract, conjunctivitis, scalp pustules, breast abscesses, eczema, and skin abscesses (Møller et al., 2019). Møller et al. suspected that the source of MRSA clonal complex 398 in a Danish hospital outbreak was imported from Southeastern Asia (Møller et al., 2019). In the second of these four studies, Nielsen et al. reported a higher prevalence of MRSA and ciprofloxacin-resistant *Enterobacterales* among refugee families compared to non-immigrants (Nielsen et al., 2022). The third study reported a gradual increase in community-acquired (CA)-MRSA cases in Denmark. Notably, CA-MRSA was more likely to be asymptomatic compared to hospital-associated MRSA (HA-MRSA) (Hetem et al., 2012). Finally, a study from Norway reported that the majority of MRSA cases were associated with community acquisition, with only 21% of cases diagnosed in hospitals and only about 5% linked to long-term care institutes (Elstrøm et al., 2019).

c) *Enterococcus* spp.

We found a total of eight studies that reported cases of resistance in *Enterococcus* spp. within clinical settings, with most being resistant to vancomycin. These studies include three from Sweden (Holmbom et al., 2020; Kaarme et al., 2015; Sundvall et al., 2014), two from Denmark (Pinholt et al., 2017, 2019), two from Norway (Elstrøm et al., 2019; Thaulow et al., 2021), and one from Finland (Kanerva et al., 2012). A Danish study reported a VRE outbreak in Denmark during 2012–2015 (Pinholt et al., 2017). Using WGS, they identified *van*A-type genes in *E. faecium* as the cause of the outbreak. Other studies targeted VRE alongside other pathogens while investigating UTI (Sundvall et al., 2014; Thaulow et al., 2021) and cases of blood infection (Elstrøm et al., 2019; Holmbom et al., 2020; Kanerva et al., 2012). These studies collectively highlighted VRE as a significant contributor to UTI and blood stream infections, along with *E. coli* and *Klebsiella* spp.

We noticed potential epidemiological variation in the occurrence of VRE types across the Nordic countries. Pinholt et al. reported a gradual increase in *van*A VR-*E. faecium* incidence in the capital region of Denmark between 2012 and 2015 (Pinholt et al., 2019). In contrast, one Norwegian study found that the *van*B type was the most prevalent (~74%), with the majority (476 out of 487 total) carried by *E. faecium* (Elstrøm et al., 2019). Sweden and Finland lack recent genotyping studies, but an earlier study in Finland indicated that both *van*A and *van*B types were predominant in the country (Vuopio-Varkila et al., 1997), while a wastewater study from 2009 reported *van*B as the most prevalent type in Sweden (Sahlström et al., 2009). All the studies noted that nosocomial VRE cases are predominant in the region (Elstrøm et al., 2019; Kanerva et al., 2012; Pinholt et al., 2019).

3.3. Wastewater monitoring for resistant bacteria in the Nordic countries

In this review, a total of 26 papers focused on monitoring wastewater for antibiotic-resistant bacteria (ARB). The vast majority of these studies were conducted in Sweden (n = 10) (Bengtsson-Palme et al., 2016; Flach et al., 2021; Huijbers et al., 2019, 2020; Hutinel et al., 2019, 2022; Iversen et al., 2002; Khan et al., 2018, 2019; Kwak et al., 2015), Finland (n = 9) (Heljanko et al., 2023; Huijbers et al., 2020; Karkman et al., 2016; Laht et al., 2014; Majlander et al., 2021; Markkanen et al., 2023; Pärnänen et al., 2019; Tiwari et al., 2022b, 2023b), and Norway (n = 9) (Cacace et al., 2019; Grevskott et al., 2021; Huijbers et al., 2020; Marathe et al., 2021; Pärnänen et al., 2019; Paulshus et al., 2019a, 2019b; Radisic et al., 2023), as detailed in Fig. 3. Denmark contributed three studies (Brinch et al., 2020; Huijbers et al., 2020; Jakobsen et al., 2008),

while Iceland did not have any studies reporting ARB or related genes in wastewater, except for participation in two global studies (Hendriksen et al., 2019; Munk et al., 2022). Notably, some studies targeted more than one country (Huijbers et al., 2020; Pärnänen et al., 2019). Most of the studies collected wastewater samples from larger cities or the capital regions. Regarding the monitoring targets, similarly to clinical studies, wastewater monitoring primarily focused on *Enterobacterales*, particularly *E. coli*, *K. pneumoniae*, and *C. freundii*, which were the subjects of 17 out of 25 studies (60.0%) (Flach et al., 2018, 2021; Grevskott et al., 2021; Heljanko et al., 2023; Huijbers et al., 2020; Hutinel et al., 2019; Jakobsen et al., 2008; Jørgensen et al., 2017; Khan et al., 2018, 2019; Kwak et al., 2015; Marathe et al., 2021; Paulshus et al., 2019a, 2019b; Radisic et al., 2023; Tiwari et al., 2022b, 2023b).

The monitoring of ARB in wastewater typically falls into two main categories: (a) analysis of wastewater influent samples from wastewater treatment plants (WWTPs) or raw sewage from healthcare settings (e.g., healthcare centers, nursing homes, or hospitals) and (b) monitoring of effluent samples, either alone or in combination with influent samples, and/or with recipient water bodies. Wastewater influent samples were analyzed with the aim of monitoring ARB pathogens in the sewer-shed community or within healthcare facilities as wastewater-based surveillance (Table S3). Monitoring of wastewater influent and effluent can enable the decay of ARB and related genes within WWTPs to be assessed and the potential public or environmental health risks after their release into surface waters to be evaluated. Monitoring of ARB and ARGs in surface waters can have the OneHealth objective of examining the AMR risks in human, animal, and environmental health.

a) Monitoring of wastewater influents

Many of the reviewed studies monitored wastewater influent or raw sewage from human health care settings to reveal the prevalence of ARB pathogens and related genes in sewershed communities (Brinch et al., 2020; Flach et al., 2021; Grevskott et al., 2021; Heljanko et al., 2023; Huijbers et al., 2020; Hutinel et al., 2019, 2022; Kwak et al., 2015; Majlander et al., 2021; Markkanen et al., 2023; Paulshus et al., 2019a,b; Tiwari et al., 2022a; Tiwari et al., 2023b). Monitoring of wastewater influent was primarily conducted for WBS, which is a non-invasive, cost-effective tool to monitor ARB pathogens and ARGs at the population level (Grevskott et al., 2021; Hendriksen et al., 2019; Hutinel et al., 2022; Karkman et al., 2020; Kwak et al., 2015; Pärnänen et al., 2019). Many studies reported new ARGs or multilocus sequence types of pathogens in wastewater monitoring that had not previously been reported in clinical surveillance in the country (Marathe et al., 2021; Paulshus et al., 2019b, 2023). ARB pathogens and their genetic markers can be released (via feces, urine, skin lesions, nasal secretions, and sputum) to the sewage system soon after the beginning of colonization and during the infections (e.g., symptomatic or asymptomatic) (Hammerum et al., 2007; Hutinel et al., 2019; Jørgensen et al., 2017).

Wastewater monitoring enabled the prevalence of ARGs and circulating sequence types of a particular pathogen to be determined. For example, Paulshus et al. reported the circulation of two different *E. coli* clones belonging to ST131 and ST648 carrying $bla_{\text{CTX-M-15}}$ by collecting wastewater samples from wastewater pump stations in Oslo, Norway (Paulshus et al., 2019b). Grevskott et al. reported antibiotic resistance profiles and the diversity of β-lactamases in *E. coli* isolates in wastewater influent in Bergen, Norway (Grevskott et al., 2021). By using WGS, Grevskott et al. reported $bla_{\text{NDM-6}}$, $bla_{\text{VIM-1}}$, $bla_{\text{OXA-48}}$, $bla_{\text{CTX-M-15}}$, $bla_{\text{CTX-M-27}}$, and $bla_{\text{CTX-M-14}}$ as the main beta-lactamase gene types (Grevskott et al., 2021). They reported sixteen *E. coli* sequence types (STs), including ST131 (39.1%), ST38 (10.9%), and ST69 (8.7%) (Grevskott et al., 2021). Most of these reported STs and ARGs are frequently found in clinical specimens in all the Nordic countries (Gladstone et al., 2021; Paulshus et al., 2019b; Roer et al., 2017).

Many of these studies compared the prevalence of ARB and related genes in municipal wastewater with nearby hospital wastewater (Flach et al., 2021; Heljanko et al., 2023; Hutinel et al., 2019; Iversen et al., 2002; Kwak et al., 2015). These studies reported generally higher resistance rates in hospital wastewater than in municipal wastewater (Hutinel et al., 2019; Iversen et al., 2002; Kwak et al., 2015). Hospitals may use a greater amount and wider spectrum of antibiotics for treating their clinical patients than are consumed in communities (ECDC, 2020). Thus, this could be the explanation behind the findings reported by Kwak et al. from Stockholm, Sweden, where the prevalence of ESBL-producing *E. coli* in hospital raw sewage (13%) was higher than in respective municipal wastewater influent (2.3%) (Kwak et al., 2015).

One study from Gothenburg, Sweden, compared ARG profiles in hospital wastewater with clinical isolates from the same hospital and reported concordance in the detection of bla_{NDM}, $bla_{\text{OXA-48-like}}$, and bla_{KPC} in both wastewater and clinical samples (Flach et al., 2021). However, bla_{VIM} and bla_{IMP} were only detected in wastewater samples, which was suspected to be due to their long persistence in the sewage networks. Another study conducted in Gothenburg, Sweden, with high-throughput qPCR also reported concordance in the detection of ARGs *mcr-1, mcr-3, mcr-4, mcr-5, sul4,* and *gar* in both hospital and municipal wastewater, but *optr*A and *cfr*(A) were only detected in hospital wastewater, and *mcr-3* and *mcr-5* were more abundant in municipal wastewater (Hutinel et al., 2022).

A study from Denmark compared gentamicin-resistant *E. coli* isolates from municipal influent and clinical isolates from hospitals and reported concordance of the *aac* (3)-II gene in both clinical and wastewater isolates in 2002–2003 (Jakobsen et al., 2008). For community-acquired cases, ARG and ARB counts may be higher in municipal wastewater than in hospital wastewater. An earlier study in Stockholm and Uppsala detected a higher prevalence of VRE in municipal wastewater compared to hospital sewage (Iversen et al., 2002).

When used at the European continental level, WBS provided concordant results compared to clinical studies. In general, Europe has low-to-high gradients of ARB and ARGs from north to south and from west to east (WHO-ECDC, 2022). In concordance with clinical reporting, a low prevalence of ARB and ARGs was reported in Nordic wastewater, with different gene clusters in Finland, Norway, and Germany versus Portugal, Spain, and Cyprus (Pärnänen et al., 2019). A lower relative abundance of ARGs related to aminoglycosides, sulfonamides, β-lactams, quinolones, amphenicols, and multidrug resistance together with genes related to mobile genetic elements in wastewater samples was reported in Finland and Norway than in European countries with a relatively high level of antibiotic consumption (Portugal, Spain, Cyprus, and Ireland) (Pärnänen et al., 2019). However, Cacace et al. did not observe clear geographical variation in different ARGs (related to bla_{TEM}, $bla_{\text{OXA-48}}$, $bla_{\text{OXA-58}}$, $bla_{\text{CTX-M-15}}$, $bla_{\text{CTX-M-32}}$, $bla_{\text{KPC-3}}$, *sul*1, *tet*M, *mcr*-1) in wastewater samples from ten European countries (France, Italy, Norway, Portugal, Germany, the Netherlands, Cyprus, Turkey, Austria, and the United Kingdom) (Cacace et al., 2019).

b) Monitoring of wastewater effluent and environmental release

Wastewater treatment can be an important process for controlling the environmental dissemination of ARB and ARG from municipal wastewater. Regular monitoring of ARB and ARGs from wastewater effluent can help in predicting the public health risk of such pathogens and genes. In this systematic review, a total of 13 studies analyzed municipal wastewater effluent together with or without influent or recipient water in monitoring ARB, ARGs, and mobile genetic elements (MGEs) (Bengtsson-Palme et al., 2016; Cacace et al., 2019; Flach et al., 2018; Grevskott et al., 2021; Hutinel et al., 2022; Iversen et al., 2002; Jørgensen et al., 2017; Karkman et al., 2016; Khan et al., 2018, 2019; Laht et al., 2014; Pärnänen et al., 2019; Paulshus et al., 2019a, 2019b; Radisic et al., 2023). The environmental release of treated wastewater was reported to increase the prevalence of ARB, ARGs, and MGEs carrying the resistome to the recipient surface water (Cacace et al., 2019; Karkman et al., 2016; Lai et al., 2021). Although WWTPs significantly

reduce such ARB, ARGs, and MGEs, an increase in the biological treatment steps in WWTPs can enrich certain ARGs in the effluent (Bengtsson-Palme et al., 2016; Cacace et al., 2019; Flach et al., 2018; Karkman et al., 2016). In addition, wastewater contains traces of diverse antimicrobial compounds from various sources, such as discarded antibiotics, detergents, heavy metals, and pesticides. Such antimicrobial compounds can also have roles in the enrichment of resistant bacteria.

Karkman et al. suspected WWTP could enrich the prevalence of two gene types, *Tn25* type transposase and clinical class 1 integrons (Karkman et al., 2016). This enrichment of class 1 integrons in wastewater treatment plants raises concerns about the possible spread of ARGs within these facilities through horizontal gene transfer. Another study found varying ratios of cefotaxime-resistant *E. coli* to total *E. coli* in influents (0.3%–4.4%) and effluents (0%–5.0%) across different samples (Grevskott et al., 2021). Laht et al. noted potential variations in ARG reduction across different WWTPs (Laht et al., 2014). They compared ARG reduction in three WWTPs from Helsinki, Tallinn, and Tartu by targeting *sul1* and *sul2* (sulphonamide-related), *tetM* and *tetC* (tetracycline-related), and $bla_{\text{OXA-58}}$, $bla_{\text{SHV-34}}$, and $bla_{\text{CTX-M-32}}$(ESBL related) with qPCR, and reported a higher reduction in WWTP in Finland than in Estonia (Laht et al., 2014). In addition, the efficiency of ARG reduction in WWTPs may vary for different genes. For example, Hutinel et al. demonstrated a high prevalence of ARGs (per bacterial 16S rRNA gene) related to colistin (*mcr-3, mcr-4, mcr-5*), sulfonamide (*sul4*), and aminoglycoside (*gar*) in treated municipal wastewater (Gothenburg, Sweden), but not for ARGs related to linezolid (*optr*A and *cfr*(A)) and colistin (*mcr-1*) (Hutinel et al., 2022).

However, a study conducted in Gothenburg, Sweden, reported that wastewater treatment plants neither enrich nor exert selective pressure on the resistance profile of *E. coli* (Flach et al., 2018). A total of 4028 *E. coli* isolates were collected from both influent and effluent and their antibiotic resistance to eight antibiotics was assessed: ampicillin, cefpodoxime, ciprofloxacin, gentamicin, sulfamethoxazole, tetracycline, and trimethoprim (Flach et al., 2018). Bengtsson-Palme et al. used metagenomics to demonstrate that wastewater treatment plants do not significantly enrich or select for ARG proliferation (Bengtsson-Palme et al., 2016). They sampled wastewater in various treatment stages from three Swedish treatment plants. Resistance genes linked to antibiotics, biocides, and metals did not decrease as much as fecal bacteria during treatment. In summary, these conflicting results in various WWTPs in Finland, Sweden, and Estonia regarding the gene enrichment of various ARGs and ARB imply inconsistency across facilities. The enrichment effect on bacteria and ARGs can vary based on treatment processes and conditions.

The release of ARGs and MGEs from wastewater treatment plants (WWTPs) can be influenced by numerous factors, including the initial loads from influent, as well as interactions with other bacterial communities and potential horizontal gene transfer (HGT) events within the biological treatment processes in WWTPs (Cacace et al., 2019). Khan et al. reported high variation in β-lactamase types in hospital wastewater and downstream recipient river water (Khan et al., 2019). They reported a high prevalence of $bla_{\text{IMP-1}}$, $bla_{\text{IMP-2}}$, and $bla_{\text{OXA-23}}$ in hospital wastewater and $bla_{\text{OXA-48}}$, $bla_{\text{CTX-M-8}}$, $bla_{\text{SFC-1}}$, $bla_{\text{VIM-1}}$, and $bla_{\text{VIM-13}}$ in downstream recipient river samples. These findings underscore the complexity of ARG release from WWTPs, with variations in ARG profiles and prevalence observed across different locations and types of wastewaters, highlighting the importance of monitoring and understanding the factors influencing the dissemination of antibiotic resistance in environmental settings.

c) ARB and ARG release to surface water

ARB and ARGs are emerging pollutants in surface water (Jørgensen et al., 2017; Khan et al., 2018; Lai et al., 2021; Radisic et al., 2023). Monitoring of ARB and ARGs in surface water serves a One Health purpose by assessing AMR risks to human, animal, and environmental health. Apart from wastewater effluent, surface water can receive such bacteria and genes from surface water runoff. For example, one study from Sweden reported a high diversity of ARGs and anthropogenic pollutant indicator genes *intI*, *sul1*, and crAssphage in surface water near large urban areas (Lai et al., 2021). Another study from Örebro, Sweden, reported the prevalence of *K. oxytoca* carrying $bla_{\text{VIM-1}}$ and $bla_{\text{IMP-29}}$ types of carbapenemase in recipient river water (Khan et al., 2018). Similarly, a study from Bergen, Norway, reported multi-drug resistant (MDR) *K. pneumoniae* in coastal water potentially contaminated with the outfall of treated effluent (Radisic et al., 2023). MDR *K. pneumoniae* of the types ST730 and ST307 were mainly reported, carrying $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-15}}$, *qnrS1*, *aac* (3)-lle, *tet*(A), and *sul1* (Radisic et al., 2023).

The occurrence of resistant profiles in surface water can sometimes be many times higher than in nearby wastewater samples. For example, one study from Oslo, Norway, reported that up to 3.8% of *E. coli* isolates were related to ESBL in recreational samples, but only about 0.56–0.75% of *E. coli* isolates from respective wastewater samples belonged to ESBL (Jørgensen et al., 2017). This might indicate the environmental dissemination of genes and also the longer persistence of resistant bacteria in the environment. This could imply various persistence rates for different *E. coli* strains (Jørgensen et al., 2017). However, a Danish study reported a relatively low prevalence (1 of 37 tested samples) of VRE in surface water compared to influent (21 of 35 samples), hospital sewage (5 of 14 samples), and effluent (6 of 32 samples). The reason could be that enteric pathogens rapidly decrease as soon as they reach the ambient environment and ARGs can rapidly emerge in the environment through the process of HGT of MGE.

4. Discussion

Wastewater surveillance for AMR primarily focuses on four areas: (a) assess AMR status in human populations and compare it using wastewater-based epidemiology (WBE), (b) identify AMR escaping wastewater treatment, (c) quantify removal rates, and (d) assess the potential for AMR evolution. Nordic countries have focused their WWS of AMR in all these four directions. Wastewater monitoring can be an important tool for the monitoring and early identification of ARB pathogen hot spots, and their temporal and spatial trends. WBS of ARB can be a useful tool for surveilling the real-time prevalence of ARB in a cost-effective manner. Currently, regular surveillance of antibiotic resistance by monitoring wastewater is lacking globally. However, the European Commission suggests using WBS to monitor local pathogen levels in its proposed revision of the Urban Wastewater Treatment Directive (UWWTD) (EU Regulation 2020/741, 2022). The proposed directive includes provisions for analyzing influent and effluent to monitor potential ARB and ARG release from WWTPs.

The Nordic countries have been notably successful in maintaining a low prevalence of ARB pathogen cases in clinical settings compared to many other European countries (WHO-ECDC, 2022). Several factors have contributed to this achievement, including low antibiotic consumption, relatively robust sanitation facilities, excellent access to clean drinking water, and well-developed public health infrastructure (Collignon et al., 2018). Additionally, these countries have implemented comprehensive strategies to combat AMR, including the establishment of national action plans for AMR, robust national surveillance systems, and the implementation of infection prevention and control (IPC) measures in both human and veterinary domains (Fig. 1, Table 1). The unnecessary use of antibiotics is avoided by emphasizing good diagnostic tools, good infection prevention, and control (IPC) practices in hospitals and veterinary settings, and the timely use of vaccines for various infections (Muray et al., 2022; Silva et al., 2021; Sternberg-Lewerin et al., 2022; Time and Veggeland, 2020). Moreover, antibiotic usage in these countries is highly regulated, antibiotics can only be purchased with prescriptions from doctors or veterinarians, and the use of antibiotics for growth promotion is prohibited in farm animals (Björkman et al., 2021; EC, 2020; Time and Veggeland, 2020). The

Nordic countries boast national healthcare insurance systems that cover all residents, accompanied by well-structured clinical data storage and management practices. These countries are strongly linked to the EU member states (Denmark, Finland, and Sweden) or the EEA agreement (Norway and Iceland).

In recent years, all the Nordic countries have consistently faced a common problem of increasing ARB and ARG cases, mainly carbapenemase and ESBL producing *Enterobacterales*, and MRSA due to international travel, hospitalization abroad, and immigration from countries with a high prevalence of ARB (Elstrøm et al., 2019; Espenhain et al., 2018; Ferløv-Schwensen et al., 2017; Gladstone et al., 2021; Helgason et al., 2016; Ingefors et al., 2022; Kanerva et al., 2015; Møller et al., 2019; Nielsen et al., 2022; Pinholt et al., 2019; Räisänen et al., 2020; Southon et al., 2020). The emergence of resistance within the *Enterobacteriaceae* family is apparent in both clinical and wastewater monitoring (Flach et al., 2021; Heljanko et al., 2023; Hutinel et al., 2019; Iversen et al., 2002; Kwak et al., 2015). The small population sizes of these countries, with shared similarities, can favor Nordic collaboration in developing and using the WBS approach for ARB and related genes. These countries have a long tradition of mutual learning through Nordic cooperation forums (Björkman et al., 2021), which may lead to the diffusion of cross-border ARB management policies. For example, clinical microbiologists collaborate on ARB management practice through the Nordic Committee on Antimicrobial Susceptibility Testing (NordicAST) (NordicAST, 2023). Furthermore, the EARS-Net EU/EEA-level consortium handles resistance surveillance, treatment guidelines, and monitoring of antibiotic consumption. In the spirit of establishing the Nordic countries as a best-practice region for surveillance, and preparing for possible worse future situations, these regions could establish an environmental surveillance network for sharing technology, understanding, and achievements at the regional level. The strategies of the Nordic countries aim to foster global and regional cooperation for surveillance (Finnish Strategy, 2023; Norwegian Ministries, 2015; Swidish Strategy, 2023).

ARB is a One-Health concern: the enrichment of such pathogens and genes in any one of the compartments (people, animals, and environment) can easily lead to them jumping to the next and collectively amplifying in all three compartments. The development of resistant mechanisms in pathogens in animals and the environment can easily reach the human community via drinking water production and distribution (Lai et al., 2021; Tiwari et al., 2022c), food animals (Al-Mustapha et al., 2023; Bhowmick et al., 2023; Hansen et al., 2016), companion animals (Hansen et al., 2016), the hospital environment (Giri et al., 2022; Heljanko et al., 2023), recreational water (Jørgensen et al., 2017; Khan et al., 2018), and seafood (Håkonsholm et al., 2022).

4.1. Monitoring methods

Wastewater surveillance of ARB is typically conducted with three monitoring methods: culture-based, qPCR, and metagenomics approaches (Karkman et al., 2018; Tiwari, et al., 2022a). Each method has its pros and cons. Culture-based methods are cost-effective, clinically validated, and useful for detecting viable targeted bacteria. They also facilitate antimicrobial susceptibility testing (AST), whole genome sequencing, and the linkage of phenotypic and genotypic traits through DNA extraction from selected isolates, enabling gene prevalence assessment. However, culture-based methods are time-consuming due to cultivation requirements (Karkman et al., 2018; Tiwari et al., 2021b), and cannot monitor viable but unculturable bacteria (Pitkänen et al., 2013; Rytkönen et al., 2021).

Culture-independent methods primarily focus on monitoring ARGs as evidence of ARB. These approaches account for all resistance genes that are carried by pathogenic or non-pathogenic strains. Molecular methods, including real-time PCR (qPCR), digital PCR (dPCR), and high-throughput qPCR (HT-qPCR), offer speed and sensitivity, complementing culture-based techniques rather than replacing them (Karkman et al., 2016, 2018). PCR-based methods require prior knowledge of primer sequences, making them suitable for the routine surveillance of known ARGs but less effective in the early detection of emerging ones (Tiwari et al., 2023a).

Metagenomics works independently on prior knowledge about the primers and provides an inventory of all ARGs or bacterial communities (Berbers et al., 2020; Tiwari et al., 2022c). Long-read sequencing adds extra insights by pinpointing gene locations, whether in plasmids or chromosomes (Berbers et al., 2020). While metagenomics provides broader ARG coverage, qPCR methods are better at detecting minor gene changes with higher sensitivity. Metagenomics is more suitable for a non-targeted screening test, but qPCR can be more suitable for the regular surveillance of ARGs (Ferreira et al., 2023). However, both PCR-based and metagenomics methods have limitations, as they cannot establish clinical breakpoints and they do not distinguish between living and dead cells. These methods cannot identify the source of specific pathogens carrying detected ARGs in wastewater. However, identifying the precise pathogen resistant to antibiotics is crucial for environmental remediation and infection treatment.

These three major ARB-monitoring methods (culturing, PCR-based, and metagenomics) each capture different aspects of ARB presence (Karkman et al., 2018; Pruden et al., 2021; Tiwari et al., 2022a). They offer unique advantages and limitations, and it is unlikely that any one of them will fully replace the others soon (Karkman et al., 2018; Tiwari et al., 2022a). Consequently, these methods are expected to remain valuable tools for years to come. Currently, comparing and disseminating results obtained through these three distinct methods can be challenging. However, conducting regular calibration studies, where the same samples are simultaneously assessed using all three methods, can significantly facilitate the exchange of research findings derived from these diverse approaches.

A critical challenge in WWS of ARB is effectively presenting quantitative data (gene copies or colony counts), due to variable levels of target material dilution in wastewater samples. One potential solution is the normalization of ARB/ARG data with the total bacterial population/or total 16S rRNA genes (Karkman et al., 2018; Pärnänen et al., 2019). Another option could be to normalize data with the flow rate in wastewater influent and the total population in the city, expressing the results as colonies or GC/person/unit time (Tiwari et al., 2022d). The same challenge also applies to metagenomics, and the normalization of its data is equally complicated (Ng et al., 2017).

4.2. Sanitation conditions in polar communities

Overall, the Nordic countries have the best sanitation infrastructures in the world. However, in some remote northern communities, wastewater treatment faces challenges due to factors such as permafrost, hard rock surfaces, spring flooding, dispersed settlements, limited water availability, and the high costs of fuel, electricity, and transportation (Gunnarsdóttir et al., 2013). Consequently, polar communities may experience inadequate wastewater treatment, which can degrade surface water quality, including the presence of ARB and various human pathogens (Lamba et al., 2018). Sewage serves as an important source for introducing clinically relevant pathogens and antibiotic resistance genes (ARGs) into the environment (Karkman et al., 2020; Marathe et al., 2021). The cold, dark, snow-covered winters in the Nordic region contribute to the prolonged persistence of these pathogens and ARB (Tiwari et al., 2023c).

In arctic coastal regions, where the fishing industry plays a pivotal role, poor sanitation in the marine environment poses a substantial public health risk due to enteric bacteria (*Salmonella, Shigella,* and *E. coli*), viral pathogens (norovirus, adenovirus, poliovirus hepatitis A and sapovirus), and protozoan parasites (*Cryptosporidium* and *Giardia*). For example, Håkonsholm et al. detected widespread MDR *K. pneumoniae* in bivalve mollusks collected from coastal areas of Norway (Håkonsholm et al., 2022).

5. Limitations and challenges of WBS

5.1. Bloodstream infection and WBS

Current clinical reporting practices for ARB often rely on isolates from invasive samples (blood and cerebrospinal fluid) from clinical settings. However, WBS offers a broader perspective, considering the overall population-level burden, and mostly but not solely accounting for ARB pathogens originating from fecal and urinary sources. This raises concerns about the shedding of ARB in the feces and urine of individuals with bloodstream infections. One Swedish study demonstrated a strong positive correlation between the resistance rate in hospital sewage and hospital clinical patients ($r^2 = 0.95$ for urine and 0.89 for blood samples) (Hutinel et al., 2019). The correlation between primary care urine samples and municipal sewage was $r^2 = 0.82$. Therefore, ARB monitoring in wastewater can represent well the ARB infection cases of bloodstream infections (Hutinel et al., 2019).

The human gut serves as a reservoir of ARB, and oral antibiotic consumption can exert selective ecological pressure on gut ARB, leading to an increase in their numbers within the gut and potential release into the sewage system (Hutinel et al., 2019). Further empirical evidence is required to support the hypothesis linking resistance in blood infections, antibiotic consumption, and selective pressure on gut bacteria for proliferation. In addition, significant quantities of resistant bacteria are potentially also harbored by healthy individuals who have not recently been exposed to antibiotics but might have been exposed through contaminated food and water (Al-Mustapha et al., 2023; Bhowmick et al., 2023; Tiwari et al., 2022c; Ulstad et al., 2016). Once bacteria acquire resistance through mobile genetic elements, this capacity can transfer both vertically to daughter cells during bacterial reproduction and horizontally to nearby cells.

5.2. Diversity and dilution

Surveillance and standardization of WBS face a significant challenge due to the diverse array of ARB and ARGs that require monitoring. Such diverse ARB pathogens and their distinct variants can have a unique loading in clinically infected individuals and a unique fate and decay rate in the wastewater distribution system (Larsson et al., 2023; Milligan et al., 2023).

Further dilution of ARB in sewage systems may reduce the target concentration below the detectable limit, resulting in a lower recorded prevalence rate. For example, Huijbers et al. reported consistently lower resistance profiles of *E. coli* isolates collected in wastewater (Table S4) than those reported by the EARS-Net surveillance mechanism in different European countries (Table 2) (Huijbers et al., 2020). They followed the same monitoring protocol as EUCAST, which EARS-Net prescribes for monitoring clinical specimens. The lower detection rate in wastewater could be due to the different monitoring matrices (invasive sample versus load from feces and urine) or due to dilution in the sewage system.

The representativeness of the microbial target monitored with WBS across the total load of the target in the entire sewage can be questioned. For example, Paulshus et al. isolated less than 100 bacterial isolates by analyzing 2.5 μl of sewage out of roughly 290,000 m^3 of wastewater influent passing through the WWTP each day (Paulshus et al., 2019a). On average, they sampled one bacterium out of every 10^{14} bacteria to make their conclusion. This applies to all WBS studies monitoring ARB. To address such limitations, 24-h composite samples are often collected. In the future, more studies may need to assess the representativeness of wastewater samples across the total wastewater volume.

5.3. Sewage comes from multiple sources, not only from human excretion

AMR is a complicated One-Health issue, many ARGs are commonly shared between humans and animals, and it is still not clear who is the primary host of these ARGs. Therefore, it is difficult to confirm an isolate or ARG monitored in wastewater and to connect it to human sources. Moreover, the sewage system, with its diverse range of antimicrobial agents (detergents, pesticides, heavy metals, chlorinated compounds) and the disposal of unused antibiotics, creates a complex environment that exerts ecological pressure, fostering the proliferation of resistant bacteria (Andersson and Hughes, 2014). The presence of such developed ARB in wastewater distribution systems can potentially lead to false positive impressions regarding ARB prevalence in the human community during WBS. In addition, many ARGs, such as β-lactamase genes have the potential to transfer via mobile genetic elements through horizontal gene transfer. Their abundance in sewage may pose a risk of horizontal gene transfer of resistant genes (Barancheshme and Munir, 2018). Therefore, the detection of ARGs in sewage samples does not guarantee release from human cases, but they can also be transferred from many intermediate hosts before being detected in certain isolates (Castañeda-Barba et al., 2023).

5.4. Standardization can be a good future option

Developing indicator pathogens can be a way to standardize ARB monitoring for WBS. ARB pathogens such as *E. coli, K. pneumoniae, Aeromonas* spp., *P. aeruginosa, E. faecalis*, and *E. faecium* can be potential indicator pathogens in WBS (Berendonk et al., 2015; Tiwari et al., 2022a). The WHO Tricycle Protocol recognizes ESBL *E. coli* as an excellent AMR indicator in One Health (WHO, 2021). The issue is how representative these indicators are of the overall ARB in the community. One earlier study reported a positive association between the prevalence of antibiotic resistance in *E. coli* from wastewater samples collected from ten European cities separately and clinical cases in the respective country (Huijbers et al., 2020). Another study reported that ten ARGs, namely bla_{TEM}, bla_{OXA-48}, bla_{OXA-58}, $bla_{CTX-M-15}$, $bla_{CTX-M-32}$, bla_{KPC-3}, *sul*1, *tet*M, and *mcr*-1, including class 1 integron integrase *int*I1, can be relevant indicators of the resistome of different environments (Berendonk et al., 2015; Rocha et al., 2020). The *int*I1 gene, encoding the class 1 integron integrases, is highly abundant in both wastewater and freshwater environments and is therefore commonly used as an indicator of anthropogenic pollution because of the linkage to gene cassettes containing genes conferring resistance to antibiotics (Karkman et al., 2018, 2020).

6. Limitations of the current study

When interpreting the conclusions of this type of systematic review, several limitations need to be considered. The reviewed literature exhibits significant heterogeneity in terms of sample sizes, targets, and detection methods. Target selection bias, especially in PCR-based methods, may occur, as primers could be designed based on perceived importance or availability. Additionally, transparency in reporting can often be lacking. Potential biases, including selection bias during keyword choice and paper screening, inclusion biases paper published only in English, as well as information and confounding biases, should be considered. Reporting biases may also exist, with positive results being more frequently published than negative ones.

7. Conclusion

The silent pandemic of AMR is an important global concern. Pathogens do not recognize the political borders of countries, making international collaboration essential. Coordinated AMR surveillance and control strategies are needed at the global, regional, and local levels. The Nordic countries , which have many similarities, can lead in AMR wastewater surveillance by adopting common strategies, aligning with EU regulations, and adhering to shared sewage effluent quality standards. Standardized methodologies can help in the comparison of spatial and temporal trends in ARB and related genes in wastewater monitoring.

Sewage analysis for ARB and ARGs complements traditional clinical resistance surveillance. It reveals spatial and temporal patterns in common ARB and ARG spread and offers early detection of rare resistance. However, precise evaluation and interpretation are crucial for a comprehensive understanding of WWS. This approach effectively communicates real-time ARB situations to diverse stakeholders, including researchers, clinicians, pharmaceutical developers, and veterinarians.

Declaration

Availability of data

The produced data have been processed and made available in the article and supplemental material.

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Competing interests

The authors declare that they have no competing interests.

Ethical approval

This study does not require ethical approval.

CRediT authorship contribution statement

Ananda Tiwari: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Adriana Krolicka:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Tam T. Tran:** Writing – review & editing, Investigation. **Kati Räisänen:** Writing – review & editing, Investigation. **Ásta Margrét Ásmundsdóttir:** Funding acquisition. **Odd-Gunnar Wikmark:** Writing – review & editing. **Rolf Lood:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Tarja Pitkänen:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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References

Aarestrup, F.M., Woolhouse, M.E.J., 2020. Using sewage for surveillance of antimicrobial resistance. Science (New York, N.Y.) 367 (6478), 630–632. https://doi.org/10.1126/science.aba3432.

Al-Mustapha, A.I., Raufu, I.A., Ogundijo, O.A., Odetokun, I.A., Tiwari, A., Brouwer, M.S. M., Adetunji, V., Heikinheimo, A., 2023. Antibiotic resistance genes, mobile elements, virulence genes, and phages in cultivated ESBL-producing *Escherichia coli* of poultry origin in Kwara State, North Central Nigeria. Int. J. Food Microbiol. 389, 110086 https://doi.org/10.1016/j.ijfoodmicro.2023.110086.

Andersson, D.I., Hughes, D., 2014. Microbiological effects of sublethal levels of antibiotics. Nat. Rev. Microbiol. 12 (7), 465–478. https://doi.org/10.1038/nrmicro3270.

Auguet, O.T., Niehus, R., Gweon, H.S., Berkley, J.A., Waichungo, J., Njim, T., Edgeworth, J.D., Batra, R., Chau, K., Swann, J., Walker, S.A., Peto, T.E.A., Crook, D. W., Lamble, S., Turner, P., Cooper, B.S., Stoesser, N., 2021. Population-level faecal metagenomic profiling as a tool to predict antimicrobial resistance in *Enterobacterales* isolates causing invasive infections: an exploratory study across Cambodia, Kenya, and the UK. EClinicalMedicine 36, 100910. https://doi.org/10.1016/j.eclinm.2021.100910.

EC, 2020. Ban on Antibiotics as Growth Promoters in Animal Feed Enters into Effect. European Commission.

Barancheshme, F., Munir, M., 2018. Strategies to combat antibiotic resistance in the wastewater treatment plants. Front. Microbiol. 8 https://doi.org/10.3389/fmicb.2017.02603.

Bengtsson-Palme, J., Hammarén, R., Pal, C., Östman, M., Björlenius, B., Flach, C.-F., Fick, J., Kristiansson, E., Tysklind, M., Larsson, D.G.J., 2016. Elucidating selection processes for antibiotic resistance in sewage treatment plants using metagenomics. Sci. Total Environ. 572, 697–712. https://doi.org/10.1016/j.scitotenv.2016.06.228.

Berbers, B., Saltykova, A., Garcia-Graells, C., Philipp, P., Arella, F., Marchal, K., Winand, R., Vanneste, K., Roosens, N.H.C., De Keersmaecker, S.C.J., 2020. Combining short and long read sequencing to characterize antimicrobial resistance genes on plasmids applied to an unauthorized genetically modified Bacillus. Sci. Rep. 10 (1), 4310. https://doi.org/10.1038/s41598-020-61158-0.

Berendonk, T.U., Manaia, C.M., Merlin, C., Kassinos, D.F., Cytryn, E., Walsh, F., Bürgmann, H., Huovinen, P., Stefani, S., Schwartz, T., Kisand, V., Baquero, F., Martinez, J.L., 2015. Tackling antibiotic resistance: the environmental framework. Nat. Rev. Microbiol. 13, 310–317. https://doi.org/10.1038/nrmicro3439.

Bhowmick, S., Pal, S., Sunder, J., Sujatha, T., De, A.K., Mondal, T., Singh, A.D., Joardar, S.N., Batabyal, K., Dutta, T.K., Bandyopadhyay, S., Tiwari, A., Samanta, I., 2023. Exploring broilers and native fowls of Andaman and Nicobar Islands as a source of β-lactamase-producing *Enterobacteriaceae* even with limited anthropogenic activities and docking-based identification of catalytic domains in novel β-lactamase variants. Front. Vet. Sci. 9 https://doi.org/10.3389/fvets.2022.1075133.

Björkman, I., Röing, M., Sternberg Lewerin, S., Stålsby Lundborg, C., Eriksen, J., 2021. Animal production with restrictive use of antibiotics to contain antimicrobial resistance in Sweden—a qualitative study. Front. Vet. Sci. 7 https://doi.org/10.3389/fvets.2020.619030.

Blaak, H., Kemper, M.A., de Man, H., van Leuken, J.P.G., Schijven, J.F., van Passel, M.W. J., Schmitt, H., de Roda Husman, A.M., 2021. Nationwide surveillance reveals frequent detection of carbapenemase-producing enterobacterales in dutch municipal wastewater. Sci. Total Environ. 776 https://doi.org/10.1016/j.scitotenv.2021.145925.

Bowes, D.A., Darling, A., Driver, E.M., Kaya, D., Maal-Bared, R., Lee, L.M., Goodman, K., Adhikari, S., Aggarwal, S., Bivins, A., Bohrerova, Z., Cohen, A., Duvallet, C., Elnimeiry, R.A., Hutchison, J.M., Kapoor, V., Keenum, I., Ling, F., Sills, D., et al., 2023. Structured ethical review for wastewater-based testing in support of public health. Environ. Sci. Technol. 57 (35), 12969–12980. https://doi.org/10.1021/acs.est.3c04529.

Brinch, C., Leekitcharoenphon, P., Duarte, A.S.R., Svendsen, C.A., Jensen, J.D., Aarestrup, F.M., 2020. Long-term temporal stability of the resistome in sewage from Copenhagen. mSystems 5 (5). https://doi.org/10.1128/mSystems.00841-20.

Cacace, D., Fatta-Kassinos, D., Manaia, C.M., Cytryn, E., Kreuzinger, N., Rizzo, L., Karaolia, P., Schwartz, T., Alexander, J., Merlin, C., Garelick, H., Schmitt, H., de Vries, D., Schwermer, C.U., Meric, S., Ozkal, C.B., Pons, M.-N., Kneis, D., Berendonk, T.U., 2019. Antibiotic resistance genes in treated wastewater and in the receiving water bodies: a pan-European survey of urban settings. Water Res. 162, 320–330. https://doi.org/10.1016/j.watres.2019.06.039.

Carlet, J., 2012. The gut is the epicentre of antibiotic resistance. Antimicrob. Resist. Infect. Control 1 (1), 39. https://doi.org/10.1186/2047-2994-1-39.

Castañeda-Barba, S., Top, E.M., Stalder, T., 2023. Plasmids, a molecular cornerstone of antimicrobial resistance in the One Health era. Nat. Rev. Microbiol. https://doi.org/10.1038/s41579-023-00926-x.

Chau, K., Barker, L., Budgell, E., Vihta, K., Sims, N., Kasprzyk-hordern, B., Harriss, E., Crook, D., Read, D., Walker, A., Stoesser, N., 2022. Systematic review of wastewater surveillance of antimicrobial resistance in human populations. Environ. Int. 162, 107171 https://doi.org/10.1016/j.envint.2022.107171.

Collignon, P., Beggs, J.J., Walsh, T.R., Gandra, S., Laxminarayan, R., 2018. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet. Health 2 (9), e398–e405. https://doi.org/10.1016/S2542-5196(18)30186-4.

Córdoba, G., Holm, A., Hansen, F., Hammerum, A.M., Bjerrum, L., 2017. Prevalence of antimicrobial resistant *Escherichia coli* from patients with suspected urinary tract infection in primary care, Denmark. BMC Infect. Dis. 17 (1), 670. https://doi.org/10.1186/s12879-017-2785-y.

DANMAP, 2023. About DANMAP. https://www.danmap.org/about-danmap.

Di Ruscio, F., Bjørnholt, J.V., Larssen, K.W., Leegaard, T.M., Moen, A.E., de Blasio, B.F., 2018. Epidemiology and spa-type diversity of meticillin-resistant *Staphylococcus aureus* in community and healthcare settings in Norway. J. Hosp. Infect. 100 (3), 316–321. https://doi.org/10.1016/j.jhin.2017.12.019.

Diemert, S., Yan, T., 2019. Clinically unreported salmonellosis outbreak detected via comparative genomic analysis of municipal wastewater *Salmonella* isolates. Appl. Environ. Microbiol. 85 (10), 1–11. https://doi.org/10.1128/AEM.00139-19.

ECDC, 2020. *Antimicrobial Consumption in the EU/EEA – Annual Epidemiological Report 2019* (Issue November).

Edslev, S.M., Clausen, M.-L., Agner, T., Stegger, M., Andersen, P.S., 2018. Genomic analysis reveals different mechanisms of fusidic acid resistance in *Staphylococcus aureus* from Danish atopic dermatitis patients. J. Antimicrob. Chemother. 73 (4), 856–861. https://doi.org/10.1093/jac/dkx481.

Elstrøm, P., Astrup, E., Hegstad, K., Samuelsen, Ø., Enger, H., Kacelnik, O., 2019. The fight to keep resistance at bay, epidemiology of carbapenemase producing organisms (CPOs), vancomycin resistant enterococci (VRE) and methicillin resistant *Staphylococcus aureus* (MRSA) in Norway, 2006 - 2017. PLoS One 14 (2), e0211741. https://doi.org/10.1371/journal.pone.0211741.

Eriksson, B.K.G., Thollström, U.-B., Nederby-Öhd, J., Örtqvist, Å., 2019. Epidemiology and control of meticillin-resistant *Staphylococcus aureus* in Stockholm County, Sweden, 2000 to 2016: overview of a "search-and-contain" strategy. Eur. J. Clin. Microbiol. Infect. Dis. 38 (12), 2221–2228. https://doi.org/10.1007/s10096-019-03664-2.

Espenhain, L., Jørgensen, S.B., Leegaard, T.M., Lelek, M.M., Hänsgen, S.H., Nakstad, B., Sunde, M., Steinbakk, M., 2018. Travel to Asia is a strong predictor for carriage of cephalosporin resistant *E. coli* and *Klebsiella* spp. but does not explain everything; prevalence study at a Norwegian hospital 2014–2016. Antimicrob. Resist. Infect. Control 7 (1), 146. https://doi.org/10.1186/s13756-018-0429-7.

EU Regulation 2020/741, 2022. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL concerning urban wastewater treatment (recast). Off. J. Eur. Union 345 (October), 1–68.

Fang, H., Fröding, I., Gian, B., Hæggman, S., Tollström, U.-B., Ullberg, M., Nord, C.E., 2016. Methicillin-resistant Staphylococcus aureus in Stockholm, Sweden: molecular epidemiology and antimicrobial susceptibilities to ceftaroline, linezolid, mupirocin and vancomycin in 2014. J. Global Antimicrob. Resist. 5, 31–35. https://doi.org/10.1016/j.jgar.2016.01.012.

Ferløv-Schwensen, S.A., Sydenham, T.V., Hansen, K.C.M., Hoegh, S.V., Justesen, U.S., 2017. Prevalence of antimicrobial resistance and the cfiA resistance gene in Danish *Bacteroides fragilis* group isolates since 1973. Int. J. Antimicrob. Agents 50 (4), 552–556. https://doi.org/10.1016/j.ijantimicag.2017.05.007.

Ferreira, C., Otani, S., Aarestrup, F.M., Manaia, C.M., 2023. Quantitative PCR versus metagenomics for monitoring antibiotic resistance genes: balancing high sensitivity and broad coverage. FEMS Microb. 4 https://doi.org/10.1093/femsmc/xtad008.

FiRe, 2023. Surveillance of Antimicrobial Resistance. https://thl.fi/en/web/infectious-diseases-and-vaccinations/surveillance-and-registers/surveillance-of-antimicrobial-resistance#fire.

Flach, C.-F., Genheden, M., Fick, J., Joakim Larsson, D.G., 2018. A comprehensive screening of *Escherichia coli* isolates from Scandinavia's largest sewage treatment plant indicates No selection for antibiotic resistance. Environ. Sci. Technol. 52 (19), 11419–11428. https://doi.org/10.1021/acs.est.8b03354.

Flach, C.-F., Hutinel, M., Razavi, M., Åhrén, C., Larsson, D.G.J., 2021. Monitoring of hospital sewage shows both promise and limitations as an early-warning system for carbapenemase-producing *Enterobacterales* in a low-prevalence setting. Water Res. 200, 117261 https://doi.org/10.1016/j.watres.2021.117261.

Fladberg, Ø.A., Jørgensen, S.B., Aamot, H.V., 2017. Genotypic characterization of gentamicin and cephalosporin resistant *Escherichia coli* isolates from blood cultures in a Norwegian university hospital 2011–2015. Antimicrob. Resist. Infect. Control 6 (1), 121. https://doi.org/10.1186/s13756-017-0280-2.

Fuursted, K., Hartmeyer, G.N., Stegger, M., Andersen, P.S., Justesen, U.S., 2016. Molecular characterisation of the clonal emergence of high-level ciprofloxacin-monoresistant *Haemophilus influenzae* in the Region of Southern Denmark. J. Global Antimicrob. Resist. 5, 67–70. https://doi.org/10.1016/j.jgar.2015.12.004.

Giri, S., Ghimire, A., Mishra, A., Acharya, K., Kuikel, S., Tiwari, A., Mishra, S.K., 2022. Prevalence of Methicillin-Resistant *Staphylococcus aureus* carriage among Healthcare Workers in South Asia in non-outbreak settings: a systematic review and meta-analysis. Am. J. Infect. Control. https://doi.org/10.1016/j.ajic.2022.06.001.

Gladstone, R.A., McNally, A., Pöntinen, A.K., Tonkin-Hill, G., Lees, J.A., Skytén, K., Cléon, F., Christensen, M.O.K., Haldorsen, B.C., Bye, K.K., Gammelsrud, K.W., Hjetland, R., Kümmel, A., Larsen, H.E., Lindemann, P.C., Löhr, I.H., Marvik, Å., Nilsen, E., Noer, M.T., Corander, J., 2021. Emergence and dissemination of antimicrobial resistance in *Escherichia coli* causing bloodstream infections in Norway in 2002–17: a nationwide, longitudinal, microbial population genomic study. Lancet Microb. 2 (7), e331–e341. https://doi.org/10.1016/S2666-5247(21)00031-8.

GLASS, 2022. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022. World Health Organization.

Grevskott, D.H., Ghavidel, F.Z., Svanevik, C.S., Marathe, N.P., 2021. Resistance profiles and diversity of β-lactamases in *Escherichia coli* strains isolated from city-scale sewage surveillance in Bergen, Norway mimic clinical prevalence. Ecotoxicol. Environ. Saf. 226, 112788 https://doi.org/10.1016/j.ecoenv.2021.112788.

Gunnarsdóttir, R., Jenssen, P.D., Erland Jensen, P., Villumsen, A., Kallenborn, R., 2013. A review of wastewater handling in the Arctic with special reference to pharmaceuticals and personal care products (PPCPs) and microbial pollution. Ecol. Eng. 50, 76–85. https://doi.org/10.1016/j.ecoleng.2012.04.025.

Håkonsholm, F., Hetland, M.A.K., Svanevik, C.S., Lunestad, B.T., Löhr, I.H., Marathe, N. P., 2022. Insights into the genetic diversity, antibiotic resistance and pathogenic potential of *Klebsiella pneumoniae* from the Norwegian marine environment using whole-genome analysis. Int. J. Hyg Environ. Health 242, 113967. https://doi.org/10.1016/j.ijheh.2022.113967.

Hammerum, A.M., Heuer, O.E., Emborg, H.-D., Bagger-Skjøt, L., Jensen, V.F., Rogues, A.-M., Skov, R.L., Agersø, Y., Brandt, C.T., Seyfarth, A.M., Muller, A., Hovgaard, K., Ajufo, J., Bager, F., Aarestrup, F.M., Frimodt-Møller, N., Wegener, H.C., Monnet, D. L., 2007. Danish integrated antimicrobial resistance monitoring and research program. Emerg. Infect. Dis. 13 (11), 1633–1639. https://doi.org/10.3201/eid1311.070421.

Hammerum, A.M., Hansen, F., Olesen, B., Struve, C., Holzknecht, B.J., Andersen, P.S., Thye, A.-M., Jakobsen, L., Røder, B.L., Stegger, M., Hansen, D.S., 2015. Investigation of a possible outbreak of NDM-5-producing ST16 *Klebsiella pneumoniae* among patients in Denmark with no history of recent travel using whole-genome sequencing. J. Global Antimicrob. Resist. 3 (3), 219–221. https://doi.org/10.1016/j.jgar.2015.05.003.

Hammerum, A.M., Lauridsen, C.A.S., Blem, S.L., Roer, L., Hansen, F., Henius, A.E., Holzknecht, B.J., Søes, L., Andersen, L.P., Røder, B.L., Justesen, U.S., Østergaard, C., Søndergaard, T., Dzajic, E., Wang, M., Fulgsang-Damgaard, D., Møller, K.L., Porsbo, L.J., Hasman, H., 2020. Investigation of possible clonal transmission of carbapenemase-producing *Klebsiella pneumoniae* complex member isolates in Denmark using core genome MLST and National Patient Registry Data. Int. J. Antimicrob. Agents 55 (5), 105931. https://doi.org/10.1016/j.ijantimicag.2020.105931.

Hansen, K.H., Bortolaia, V., Nielsen, C.A., Nielsen, J.B., Schønning, K., Agersø, Y., Guardabassi, L., 2016. Host-specific patterns of genetic diversity among IncI1-Iγ and IncK plasmids encoding CMY-2 β-lactamase in *Escherichia coli* isolates from humans, poultry meat, poultry, and dogs in Denmark. Appl. Environ. Microbiol. 82 (15), 4705–4714. https://doi.org/10.1128/AEM.00495-16.

Hansen, S.K., Kaya, H., Roer, L., Hansen, F., Skovgaard, S., Justesen, U.S., Hansen, D.S., Andersen, L.P., Knudsen, J.D., Røder, B.L., Østergaard, C., Søndergaard, T., Dzajic, E., Wang, M., Samulioniené, J., Hasman, H., Hammerum, A.M., 2020. Molecular characterization of Danish ESBL/AmpC-producing *Klebsiella pneumoniae* from bloodstream infections, 2018. J. Global Antimicrob. Resist. 22, 562–567. https://doi.org/10.1016/j.jgar.2020.05.014.

Helgason, K.O., Jelle, A.E., Gudlaugsson, O., Edvardsson, V., Findlay, J., Hopkins, K.L., Woodford, N., Samuelsen, Ø., Hardarson, H.S., 2016. First detection of a carbapenemase-producing *Enterobacteriaceae* in Iceland. J. Global Antimicrob. Resist. 6, 73–74. https://doi.org/10.1016/j.jgar.2016.04.002.

Heljanko, V., Johansson, V., Räisänen, K., Anttila, V.-J., Lyytikäinen, O., Jalava, J., Weijo, I., Lehtinen, J.-M., Lehto, K.-M., Lipponen, A., Oikarinen, S., Pitkänen, T., Heikinheimo, A., 2023. Genomic epidemiology of nosocomial carbapenemase-producing *Citrobacter freundii* in sewerage systems in the Helsinki metropolitan area, Finland. Front. Microbiol. 14 https://doi.org/10.3389/fmicb.2023.1165751.

Hendriksen, R.S., Munk, P., Njage, P., van Bunnik, B., McNally, L., Lukjancenko, O., Röder, T., Nieuwenhuijse, D., Pedersen, S.K., Kjeldgaard, J., Kaas, R.S., Clausen, P.T. L.C., Vogt, J.K., Leekitcharoenphon, P., van de Schans, M.G.M., Zuidema, T., de Roda Husman, A.M., Rasmussen, S., Petersen, B., et al., 2019. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nat. Commun. 10 (1), 1124. https://doi.org/10.1038/s41467-019-08853-3.

Hetem, D.J., Westh, H., Boye, K., Jarlov, J.O., Bonten, M.J.M., Bootsma, M.C.J., 2012. Nosocomial transmission of community-associated methicillin-resistant *Staphylococcus aureus* in Danish Hospitals. J. Antimicrob. Chemother. 67 (7), 1775–1780. https://doi.org/10.1093/jac/dks125.

Hjálmarsdóttir, M.Á., Haraldsson, G., Quirk, S.J., Haraldsson, Á., Erlendsdóttir, H., Kristinsson, K.G., 2020. Reduction of antimicrobial resistant pneumococci seven years after introduction of pneumococcal vaccine in Iceland. PLoS One 15 (3), e0230332. https://doi.org/10.1371/journal.pone.0230332.

Holmbom, M., Möller, V., Nilsson, L.E., Giske, C.G., Rashid, M.-U., Fredrikson, M., Hällgren, A., Hanberger, H., Balkhed, Å.Ö., 2020. Low incidence of antibiotic-resistant bacteria in south-east Sweden: an epidemiologic study on 9268 cases of bloodstream infection. PLoS One 15 (3), e0230501. https://doi.org/10.1371/journal.pone.0230501.

Huijbers, P.M.C., Flach, C.F., Larsson, D.G.J., 2019. A conceptual framework for the environmental surveillance of antibiotics and antibiotic resistance. Environ. Int. 130 https://doi.org/10.1016/j.envint.2019.05.074.

Huijbers, P.M.C., Larsson, D.G.J., Flach, C.F., 2020. Surveillance of antibiotic resistant *Escherichia coli* in human populations through urban wastewater in ten European countries. Environ. Pollut. 261 https://doi.org/10.1016/j.envpol.2020.114200.

Hutinel, M., Huijbers, P.M.C., Fick, J., Åhrén, C., Larsson, D.G.J., Flach, C.-F., 2019. Population-level surveillance of antibiotic resistance in *Escherichia coli* through sewage analysis. Euro Surveill. 24 (37), 1–11. https://doi.org/10.2807/1560-7917.ES.2019.24.37.1800497.

Hutinel, M., Larsson, D.G.J., Flach, C.-F., 2022. Antibiotic resistance genes of emerging concern in municipal and hospital wastewater from a major Swedish city. Sci. Total Environ. 812, 151433 https://doi.org/10.1016/j.scitotenv.2021.151433.

Ingefors, E., Tverring, J., Nafaa, F., Jönsson, N., Karlsson Söbirk, S., Kjölvmark, C., Ljungquist, O., 2022. Low 30-day mortality and low carbapenem-resistance in a decade of *Acinetobacter bacteraemia* in South Sweden. Infect. Ecol. Epidemiol. 12 (1) https://doi.org/10.1080/20008686.2021.2009324.

Iversen, A., Kuhn, I., Franklin, A., Mollby, R., 2002. High prevalence of vancomycin-resistant enterococci in Swedish sewage. Appl. Environ. Microbiol. 68 (6), 2838–2842. https://doi.org/10.1128/AEM.68.6.2838-2842.2002.

Jakobsen, L., Sandvang, D., Hansen, L.H., Bagger-skjøt, L., Westh, H., Jørgensen, C., Hansen, D.S., Pedersen, B.M., Monnet, D.L., Frimodt-møller, N., Sørensen, S.J., Hammerum, A.M., 2008. Characterisation, dissemination and persistence of gentamicin resistant *Escherichia coli* from a Danish university hospital to the waste

water environment. Environ. Int. 34 (1), 108–115. https://doi.org/10.1016/j.envint.2007.07.011.
Jørgensen, S., Søraas, A., Arnesen, L., Leegaard, T., Sundsfjord, A., Jenum, P., 2017. A comparison of extended spectrum β -lactamase producing *Escherichia coli* from clinical , recreational water and wastewater samples associated in time and location. PLoS One 12 (10), e0186576. https://doi.org/10.1371/journal.pone.0186576October.
Kaarme, J., Hasan, B., Rashid, M., Olsen, B., 2015. Zero prevalence of vancomycin-resistant enterococci among Swedish preschool children. Microb. Drug Resist. 21 (1), 65–68. https://doi.org/10.1089/mdr.2014.0043.
Kanerva, Mari, Ollgren, J., Hakanen, A.J., Lyytikäinen, O., 2012. Estimating the burden of healthcare-associated infections caused by selected multidrug-resistant bacteria Finland, 2010. Antimicrob. Resist. Infect. Control 1 (1), 33. https://doi.org/10.1186/2047-2994-1-33.
Kanerva, M., Skogberg, K., Ryynänen, K., Pahkamäki, A., Jalava, J., Ollgren, J., Tarkka, E., Lyytikäinen, O., 2015. Coincidental detection of the first outbreak of carbapenemase-producing *Klebsiella pneumoniae* colonisation in a primary care hospital, Finland, 2013. Euro Surveill. 20 (26), 1–7. https://doi.org/10.2807/1560-7917.ES2015.20.26.21172.
Karkman, A., Johnson, T.A., Lyra, C., Stedtfeld, R.D., Tamminen, M., Tiedje, J.M., Virta, M., 2016. High-throughput quantification of antibiotic resistance genes from an urban wastewater treatment plant. FEMS (Fed. Eur. Microbiol. Soc.) Microbiol. Ecol. 92 (3) https://doi.org/10.1093/femsec/fiw014.
Karkman, A., Do, T.T., Walsh, F., Virta, M.P.J., 2018. Antibiotic-resistance genes in waste water. Trends Microbiol. 26 (3), 220–228. https://doi.org/10.1016/j.tim.2017.09.005.
Karkman, A., Berglund, F., Flach, C.-F., Kristiansson, E., Larsson, D.G.J., 2020. Predicting clinical resistance prevalence using sewage metagenomic data. Commun. Biol. 3 (1), 711. https://doi.org/10.1038/s42003-020-01439-6.
Khan, F.A., Hellmark, B., Ehricht, R., Söderquist, B., Jass, J., 2018. Related carbapenemase-producing *Klebsiella* isolates detected in both a hospital and associated aquatic environment in Sweden. Eur. J. Clin. Microbiol. Infect. Dis. 37 (12), 2241–2251. https://doi.org/10.1007/s10096-018-3365-9.
Khan, F.A., Söderquist, B., Jass, J., 2019. Prevalence and diversity of antibiotic resistance genes in Swedish aquatic environments impacted by household and hospital wastewater. Front. Microbiol. 10 (APR), 1–12. https://doi.org/10.3389/fmicb.2019.00688.
Korhonen, P.E., 2018. The Nordic countries on top of the world – what next? Scand. J. Prim. Health Care 36 (4), 353–354. https://doi.org/10.1080/02813432.2018.1533668.
Kostamo, P., Veijola, L., Oksanen, A., Sarna, S., Rautelin, H., 2011. Recent trends in primary antimicrobial resistance of *Helicobacter pylori* in Finland. Int. J. Antimicrob. Agents 37 (1), 22–25. https://doi.org/10.1016/j.ijantimicag.2010.09.013.
Kwak, Y.-K., Colque, P., Byfors, S., Giske, C.G., Möllby, R., Kühn, I., 2015. Surveillance of antimicrobial resistance among *Escherichia coli* in wastewater in Stockholm during 1 year: does it reflect the resistance trends in the society? Int. J. Antimicrob. Agents 45 (1), 25–32. https://doi.org/10.1016/j.ijantimicag.2014.09.016.
Laht, M., Karkman, A., Voolaid, V., Ritz, C., Tenson, T., Virta, M., Kisand, V., 2014. Abundances of tetracycline, sulphonamide and beta-lactam antibiotic resistance genes in conventional wastewater treatment plants (WWTPs) with different waste load. PLoS One 9 (8), e103705. https://doi.org/10.1371/journal.pone.0103705.
Lai, F.Y., Muziasari, W., Virta, M., Wiberg, K., Ahrens, L., 2021. Profiles of environmental antibiotic resistomes in the urban aquatic recipients of Sweden using high-throughput quantitative PCR analysis. Environ. Pollut. 287, 117651 https://doi.org/10.1016/j.envpol.2021.117651.
Lamba, M., Gupta, S., Shukla, R., Graham, D.W., Sreekrishnan, T.R., Ahammad, S.Z., 2018. Carbapenem resistance exposures via wastewaters across New Delhi. Environ. Int. 119, 302–308. https://doi.org/10.1016/j.envint.2018.07.004.
Langdon, A., Schwartz, D.J., Bulow, C., Sun, X., Hink, T., Reske, K.A., Jones, C., Burnham, C.-A.D., Dubberke, E.R., Dantas, G., 2021. Microbiota restoration reduces antibiotic-resistant bacteria gut colonization in patients with recurrent *Clostridioides difficile* infection from the open-label PUNCH CD study. Genome Med. 13 (1), 28. https://doi.org/10.1186/s13073-021-00843-9.
Larsson, D.G.J., Flach, C.-F., Laxminarayan, R., 2023. Sewage surveillance of antibiotic resistance holds both opportunities and challenges. Nat. Rev. Microbiol. 21 (4), 213–214. https://doi.org/10.1038/s41579-022-00835-5.
Löfmark, S., Sjöström, K., Mäkitalo, B., Edquist, P., Tegmark Wisell, K., Giske, C.G., 2015. Carbapenemase-producing *Enterobacteriaceae* in Sweden 2007–2013: experiences from seven years of systematic surveillance and mandatory reporting. Drug Resist. Updates 20, 29–38. https://doi.org/10.1016/j.drup.2015.05.001.
Majlander, J., Anttila, V.-J., Nurmi, W., Seppälä, A., Tiedje, J., Muziasari, W., 2021. Routine wastewater-based monitoring of antibiotic resistance in two Finnish hospitals: focus on carbapenem resistance genes and genes associated with bacteria causing hospital-acquired infections. J. Hosp. Infect. 117, 157–164. https://doi.org/10.1016/j.jhin.2021.09.008.
Marathe, N.P., Svanevik, C.S., Ghavidel, F.Z., Grevskott, D.H., 2021. First report of mobile tigecycline resistance gene tet(X4)-harbouring multidrug-resistant *Escherichia coli* from wastewater in Norway. J. Global Antimicrob. Resist. 27, 37–40. https://doi.org/10.1016/j.jgar.2021.07.019.
Markkanen, M.A., Haukka, K., Pärnänen, K.M.M., Dougnon, V.T., Bonkoungou, I.J.O., Garba, Z., Tinto, H., Sarekoski, A., Karkman, A., Kantele, A., Virta, M.P.J., 2023. Metagenomic analysis of the abundance and composition of antibiotic resistance genes in hospital wastewater in Benin, Burkina Faso, and Finland. mSphere 8 (1). https://doi.org/10.1128/msphere.00538-22.
Mehl, A., Åsvold, B.O., Kümmel, A., Lydersen, S., Paulsen, J., Haugan, I., Solligård, E., Damås, J.K., Harthug, S., Edna, T.-H., 2017. Trends in antimicrobial resistance and empiric antibiotic therapy of bloodstream infections at a general hospital in Mid-Norway: a prospective observational study. BMC Infect. Dis. 17 (1), 116. https://doi.org/10.1186/s12879-017-2210-6.
Milligan, E.G., Calarco, J., Davis, B.C., Keenum, I.M., Liguori, K., Pruden, A., Harwood, V.J., 2023. A systematic review of culture-based methods for monitoring antibiotic-resistant *Acinetobacter*, *Aeromonas*, and *Pseudomonas* as environmentally relevant pathogens in wastewater and surface water. Curr. Environ. Health Rep. 10 (2), 154–171. https://doi.org/10.1007/s40572-023-00393-9.
Miłobedzka, A., Ferreira, C., Vaz-Moreira, I., Calderón-Franco, D., Gorecki, A., Purkrtova, S., Jan, Bartacek, Dziewit, L., Singleton, C.M., Nielsen, P.H., Weissbrodt, D.G., Manaia, C.M., 2022. Monitoring antibiotic resistance genes in wastewater environments: the challenges of filling a gap in the One-Health cycle. J. Hazard Mater. 424 (Pt C), 127407 https://doi.org/10.1016/j.jhazmat.2021.127407.
Norwegian Ministries, 2015. National Strategy against Antibiotic Resistance 2015–2020. https://www.who.int/publications/m/item/norway-national-strategy-against-antibiotic-resistance.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Br. Med. J. 339 (jul21 1), b2535. https://doi.org/10.1136/bmj.b2535.
Møller, J.K., Larsen, A.R., Østergaard, C., Møller, C.H., Kristensen, M.A., Larsen, J., 2019. International travel as source of a hospital outbreak with an unusual meticillin-resistant *Staphylococcus aureus* clonal complex 398, Denmark, 2016. Euro Surveill. 24 (42) https://doi.org/10.2807/1560-7917.ES.2019.24.42.1800680.
Munk, P., Brinch, C., Moller, F.D., Petersen, T.N., Hendriksen, R.S., Seyfarth, A.M., Kjeldgaard, J.S., Svendsen, C.A., van Bunnik, B., Berglund, F., , Global Sewage Surveillance Consortium, Larsson, D.G.J., Koopmans, M., Woolhouse, M., Aarestrup, F.M., 2022. Genomic analysis of sewage from 101 countries reveals global landscape of antimicrobial resistance. Nat. Commun. 13 (1), 7251. https://doi.org/10.1038/s41467-022-34312-7.
Muray, C.J.L., Ikuta, K.S., Sharara, F., Swetschinski, L., Collaborators, A.R., 2022. Global burden of bacterial antimicrobial resistance in 2019 : a systematic analysis. Lancet 399, 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0.
Ng, C., Tay, M., Tan, B., Le, T.-H., Haller, L., Chen, H., Koh, T.H., Barkham, T.M.S., Thompson, J.R., Gin, K.Y.H., 2017. Characterization of metagenomes in urban aquatic compartments reveals high prevalence of clinically relevant antibiotic resistance genes in wastewaters. Front. Microbiol. 8 (NOV), 1–12. https://doi.org/10.3389/fmicb.2017.02200.
Nielsen, R.T., Köse, G., Sloth, L., Andersen, C.Ø., Petersen, J.H., Norredam, M., 2022. Pathogen distribution and antimicrobial resistance in infections in migrants and nonmigrants in Denmark, a cross-sectional study. Trop. Med. Int. Health 27 (11), 999–1008. https://doi.org/10.1111/tmi.13820.
Nordic cooperation, 2023. Nordic Cooperation. https://um.fi/nordic-cooperation.
NordicAST, 2023. Nordic Committee on Antimicrobial Susceptibility Testing. http://nordicast.intranet2.se/index.
NORM, 2023. Norwegian Surveillance System for Antimicrobial Drug Resistance. https://www.fhi.no/en/in/surveillance/norm/.
Österblad, M., Kirveskari, J., Hakanen, A.J., Tissari, P., Vaara, M., Jalava, J., 2012. Carbapenemase-producing *Enterobacteriaceae* in Finland: the first years (2008-11). J. Antimicrob. Chemother. 67 (12), 2860–2864. https://doi.org/10.1093/jac/dks299.
Pärnänen, K., Narciso-da-Rocha, C., Kneis, D., Berendonk, T.U., Cacace, D., Do, T.T., Elpers, C., Fatta-Kassinos, D., Henriques, I., Jaeger, T., Karkman, A., Martinez, J.L., Michael, S.G., Michael-Kordatou, I., O'Sullivan, K., Rodriguez-Mozaz, S., Schwartz, T., Sheng, H., Sørum, H., Manaia, C.M., 2019. Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. Sci. Adv. 5 (3), 9124. https://doi.org/10.1126/sciadv.aau9124.
Paulshus, E., Kuhn, I., Mollby, R., Colque, P., Sullivan, K.O., Midtvedt, T., Lingaas, E., Holmstad, R., Sorum, H., 2019a. Diversity and antibiotic resistance among *Escherichia coli* populations in hospital and community wastewater compared to wastewater at the receiving urban treatment plant. Water Res. 161, 232–241. https://doi.org/10.1016/j.watres.2019.05.102.
Paulshus, E., Thorell, K., Guzman-Otazo, J., Joffre, E., Colque, P., Kühn, I., Möllby, R., Sørum, H., Sjöling, Å., 2019b. Repeated isolation of extended-spectrum-β-lactamase-positive *Escherichia coli* sequence types 648 and 131 from community wastewater indicates that sewage systems are important sources of emerging clones of antibiotic-resistant bacteria. Antimicrob. Agents Chemother. 63 (9) https://doi.org/10.1128/AAC.00823-19.
Paulshus, E., Colque, P., Kühn, I., Tauhid, T., Hu, Y.O.O., Zhou, Y., Thorell, K., Möllby, R., Sørum, H., Sjöling, Å., Joffré, E., 2023. *Escherichia coli* ST2797 is abundant in wastewater and might Be a novel emerging extended-spectrum beta-lactamase *E. coli*. Microbiol. Spectr. https://doi.org/10.1128/spectrum.04486-22.
Pinholt, M., Gumpert, H., Bayliss, S., Nielsen, J.B., Vorobieva, V., Pedersen, M., Feil, E., Worning, P., Westh, H., 2017. Genomic analysis of 495 vancomycin-resistant *Enterococcus faecium* reveals broad dissemination of a vanA plasmid in more than 19 clones from Copenhagen, Denmark. J. Antimicrob. Chemother. 72 (1), 40–47. https://doi.org/10.1093/jac/dkw360.
Pinholt, M., Bayliss, S.C., Gumpert, H., Worning, P., Jensen, V.V.S., Pedersen, M., Feil, E. J., Westh, H., 2019. WGS of 1058 *Enterococcus faecium* from Copenhagen, Denmark, reveals rapid clonal expansion of vancomycin-resistant clone ST80 combined with widespread dissemination of a vanA-containing plasmid and acquisition of a heterogeneous accessory genome. J. Antimicrob. Chemother. 74 (7), 1776–1785. https://doi.org/10.1093/jac/dkz118.
Pitkänen, T., Ryu, H., Elk, M., Hokajärvi, A.M., Siponen, S., Vepsäläinen, A., Räsänen, P., Santo Domingo, J.W., 2013. Detection of fecal bacteria and source tracking

identifiers in environmental waters using rRNA-based RT-qPCR and rDNA-based qPCR assays. Environ. Sci. Technol. 47 (23), 13611–13620. https://doi.org/10.1021/es403489b.

Pruden, A., Vikesland, P.J., Davis, B.C., de Roda Husman, A.M., 2021. Seizing the moment: now is the time for integrated global surveillance of antimicrobial resistance in wastewater environments. Curr. Opin. Microbiol. 64, 91–99. https://doi.org/10.1016/j.mib.2021.09.013.

Radisic, V., Grevskott, D.H., Lunestad, B.T., Øvreås, L., Marathe, N.P., 2023. Sewage-based surveillance shows presence of *Klebsiella pneumoniae* resistant against last resort antibiotics in the population in Bergen, Norway. Int. J. Hyg Environ. Health 248, 114075. https://doi.org/10.1016/j.ijheh.2022.114075.

Räisänen, K., Lyytikäinen, O., Kauranen, J., Tarkka, E., Forsblom-Helander, B., Grönroos, J.O., Vuento, R., Arifulla, D., Sarvikivi, E., Toura, S., Jalava, J., 2020. Molecular epidemiology of carbapenemase-producing *Enterobacterales* in Finland, 2012–2018. Eur. J. Clin. Microbiol. Infect. Dis. 39 (9), 1651–1656. https://doi.org/10.1007/s10096-020-03885-w.

Räisänen, K., Sarvikivi, E., Arifulla, D., Pietikäinen, R., Forsblom-Helander, B., Tarkka, E., Anttila, V.-J., Grönroos, J.O., Rintala, E., Kauranen, J., Ahlsved, M., Broas, M., Mikkola, J., Sieberns, J., Jalava, J., Lyytikäinen, O., 2021. Three clusters of carbapenemase-producing *Citrobacter freundii* in Finland, 2016–20. J. Antimicrob. Chemother. 76 (10), 2697–2701. https://doi.org/10.1093/jac/dkab209.

Ramstad, S.N., Brandal, L.T., Taxt, A.M., Wasteson, Y., Bjørnholt, J.V., Naseer, U., 2021. Prevalence of genotypic antimicrobial resistance in clinical Shiga toxin-producing *Escherichia coli* in Norway, 2018 to 2020. J. Med. Microbiol. 70 (12) https://doi.org/10.1099/jmm.0.001454.

Richelsen, R., Smit, J., Anru, P.L., Schønheyder, H.C., Nielsen, H., 2020. Incidence of community-onset extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* infections: an 11-year population-based study in Denmark. Infect. Dis. 52 (8), 547–556. https://doi.org/10.1080/23744235.2020.1763452.

Rocha, J., Cacace, D., Kampouris, I., Guilloteau, H., Jäger, T., Marano, R.B.M., Karaolia, P., Manaia, C.M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Berendonk, T. U., Schwartz, T., 2020. Inter-laboratory calibration of quantitative analyses of antibiotic resistance genes. J. Environ. Chem. Eng. 8 (1), 102214 https://doi.org/10.1016/j.jece.2018.02.022.

Roer, L., Hansen, F., Thomsen, M.C.F., Knudsen, J.D., Hansen, D.S., Wang, M., Samulioniené, J., Justesen, U.S., Røder, B.L., Schumacher, H., Østergaard, C., Andersen, L.P., Dzajic, E., Søndergaard, T.S., Stegger, M., Hammerum, A.M., Hasman, H., 2017. WGS-based surveillance of third-generation cephalosporin-resistant *Escherichia coli* from bloodstream infections in Denmark. J. Antimicrob. Chemother. 72 (7), 1922–1929. https://doi.org/10.1093/jac/dkx092.

Rytkönen, A., Tiwari, A., Hokajärvi, A.-M., Uusheimo, S., Vepsäläinen, A., Tulonen, T., Pitkänen, T., 2021. The use of ribosomal RNA as a microbial source tracking target highlights the assay host-specificity requirement in water quality assessments. Front. Microbiol. 12 (1137).

Sahlström, L., Rehbinder, V., Albihn, A., Aspan, A., Bengtsson, B., 2009. Vancomycin resistant enterococci (VRE) in Swedish sewage sludge. Acta Vet. Scand. 51 (1), 24. https://doi.org/10.1186/1751-0147-51-24.

Samuelsen, Ø., Overballe-Petersen, S., Bjørnholt, J.V., Brisse, S., Doumith, M., Woodford, N., Hopkins, K.L., Aasnæs, B., Haldorsen, B., Sundsfjord, A., 2017. Molecular and epidemiological characterization of carbapenemase-producing *Enterobacteriaceae* in Norway, 2007 to 2014. PLoS One 12 (11), e0187832. https://doi.org/10.1371/journal.pone.0187832.

Samuelsen, Ø., Hansen, F., Aasnæs, B., Hasman, H., Lund, B.A., Leiros, H.-K.S., Lilje, B., Janice, J., Jakobsen, L., Littauer, P., Søes, L.M., Holzknecht, B.J., Andersen, L.P., Stegger, M., Andersen, P.S., Hammerum, A.M., 2018. Dissemination and characteristics of a novel plasmid-encoded carbapenem-hydrolyzing class D β-lactamase, OXA-436, found in isolates from four patients at six different hospitals in Denmark. Antimicrob. Agents Chemother. 62 (1) https://doi.org/10.1128/AAC.01260-17.

Silva, A.C., Nogueira, P.J., Paiva, J.-A., 2021. Determinants of antimicrobial resistance among the different European countries: more than human and animal antimicrobial consumption. Antibiotics 10 (7), 834. https://doi.org/10.3390/antibiotics10070834.

Southon, S.B., Beres, S.B., Kachroo, P., Saavedra, M.O., Erlendsdóttir, H., Haraldsson, G., Yerramilli, P., Pruitt, L., Zhu, L., Musser, J.M., Kristinsson, K.G., 2020. Population genomic molecular epidemiological study of macrolide-resistant *Streptococcus pyogenes* in Iceland, 1995 to 2016: identification of a large clonal population with a pbp2x mutation conferring reduced in vitro β-lactam susceptibility. J. Clin. Microbiol. 58 (9) https://doi.org/10.1128/JCM.00638-20.

Sternberg-Lewerin, S., Boqvist, S., Nørstebø, S.F., Grönthal, T., Heikinheimo, A., Johansson, V., Heljanko, V., Kurittu, P., Fall, N., Magnusson, U., Mohn Bjelland, A., Sørum, H., Wasteson, Y., 2022. Nordic vets against AMR—an initiative to share and promote good practices in the Nordic–Baltic region. Antibiotics 11 (8), 1050. https://doi.org/10.3390/antibiotics11081050.

Finnish Strategy, 2023. Finnish ministry of social affairs and health. Natl. Action Plan Antimicrob. Resist. 2017–2021. http://urn.fi/URN, 978-952-00-3965-3.

Sundvall, P.-D., Elm, M., Gunnarsson, R., Mölstad, S., Rodhe, N., Jonsson, L., Ulleryd, P., 2014. Antimicrobial resistance in urinary pathogens among Swedish nursing home residents remains low: a cross-sectional study comparing antimicrobial resistance from 2003 to 2012. BMC Geriatr. 14 (1), 30. https://doi.org/10.1186/1471-2318-14-30.

SWEDRESS, 2023. Swedres-Svarm Reports. https://www.sva.se/en/what-we-do/antibiotics/svarm-resistance-monitoring/swedres-svarm-reports/.

Thaulow, C.M., Lindemann, P.C., Klingenberg, C., Berild, D., Salvesen Blix, H., Myklebust, T.Å., Harthug, S., 2021. Epidemiology and antimicrobial susceptibility of invasive bacterial infections in children—a population-based study from Norway. Pediatr. Infect. Dis. J. 40 (5), 403–410. https://doi.org/10.1097/INF.0000000000003013.

Time, M.S., Veggeland, F., 2020. Adapting to a global health challenge: managing antimicrobial resistance in the Nordics. Polit. Govern. 8 (4), 53–64. https://doi.org/10.17645/pag.v8i4.3356.

Tiwari, A., Hokajärvi, A.-M., Santo Domingo, J., Elk, M., Jayaprakash, B., Ryu, H., Siponen, S., Vepsäläinen, A., Kauppinen, A., Puurunen, O., Artimo, A., Perkola, N., Huttula, T., Miettinen, I.T., Pitkänen, T., 2021a. Bacterial diversity and predicted enzymatic function in a multipurpose surface water system – from wastewater effluent discharges to drinking water production. Environ. Microbiome 16 (1), 11. https://doi.org/10.1186/s40793-021-00379-w.

Tiwari, A., Oliver, D.M., Bivins, A., Sherchan, S.P., Pitkänen, T., 2021b. Bathing water quality monitoring practices in Europe and the United States. Int. J. Environ. Res. Publ. Health 18 (11), 5513. https://doi.org/10.3390/ijerph18115513.

Tiwari, A., Kurittu, P., Al-Mustapha, A.I., Heljanko, V., Johansson, V., Thakali, O., Mishra, S.K., Lehto, K.-M., Lipponen, A., Oikarinen, S., Pitkänen, T., Heikinheimo, A., 2022a. Wastewater surveillance of antibiotic-resistant bacterial pathogens: a systematic review. Front. Microbiol. 13 https://doi.org/10.3389/fmicb.2022.977106.

Tiwari, A., Paakkanen, J., Österblad, M., Kirveskari, J., Hendriksen, R.S., Heikinheimo, A., 2022b. Wastewater surveillance detected carbapenemase enzymes in clinically relevant gram-negative bacteria in Helsinki, Finland; 2011–2012. Front. Microbiol. 13, 1–14. https://doi.org/10.3389/fmicb.2022.887888.

Tiwari, A., Gomez-alvarez, V., Siponen, S., Sarekoski, A., Hokajärvi, A., Kauppinen, A., Torvinen, E., Miettinen, I.T., Pitkänen, T., 2022c. Bacterial genes encoding resistance against antibiotics and metal in well-maintained drinking water distribution systems in Finland. Front. Microbiol. 12 (803094), 1–9. https://doi.org/10.3389/fmicb.2021.803094. February.

Tiwari, A., Lipponen, A., Hokajärvi, A.-M., Luomala, O., Sarekoski, A., Rytkönen, A., Österlund, P., Al-Hello, H., Juutinen, A., Miettinen, I.T., Savolainen-Kopra, C., Pitkänen, T., 2022d. Detection and quantification of SARS-CoV-2 RNA in wastewater influent in relation to reported COVID-19 incidence in Finland. Water Res. 215, 118220 https://doi.org/10.1016/J.WATRES.2022.118220.

Tiwari, A., Adhikari, S., Zhang, S., Solomon, T.B., Lipponen, A., Islam, M.A., Thakali, O., Sangkham, S., Shaheen, M.N.F., Jiang, G., Haramoto, E., Mazumder, P., Malla, B., Kumar, M., Pitkänen, T., Sherchan, S.P., 2023a. Tracing COVID-19 trails in wastewater: a systematic review of SARS-CoV-2 surveillance with viral variants. Water 15 (6), 1018. https://doi.org/10.3390/w15061018.

Tiwari, A., Paakkanen, J., Al-Mustapha, A.I., Kirveskari, J., Hendriksen, R.S., Heikinheimo, A., 2023b. Phenotypic and genotypic characteristics of beta-lactamase dominant with CARBA, AmpC, and ESBL-producing bacteria in municipal wastewater influent in Helsinki, Finland. J. Global Antimicrob. Resist. 33, 345–352. https://doi.org/10.1016/j.jgar.2023.04.015.

Tiwari, A., Kauppinen, A., Räsänen, P., Salonen, J., Wessels, L., Juntunen, J., Miettinen, I. T., Pitkänen, T., 2023c. Effects of temperature and light exposure on the decay characteristics of fecal indicators, norovirus, and Legionella in mesocosms simulating subarctic river water. Sci. Total Environ. 859 (Pt 2), 160340 https://doi.org/10.1016/j.scitotenv.2022.160340.

Tønnessen, R., García, I., Debech, N., Lindstrøm, J.C., Wester, A.L., Skaare, D., 2022. Molecular epidemiology and antibiotic resistance profiles of invasive *Haemophilus influenzae* from Norway 2017–2021. Front. Microbiol. 13 https://doi.org/10.3389/fmicb.2022.973257.

Tyrstrup, M., Melander, E., Hedin, K., Beckman, A., Mölstad, S., 2017. Children with respiratory tract infections in Swedish primary care; prevalence of antibiotic resistance in common respiratory tract pathogens and relation to antibiotic consumption. BMC Infect. Dis. 17 (1), 603. https://doi.org/10.1186/s12879-017-2703-3.

Ulstad, C.R., Solheim, M., Berg, S., Lindbæk, M., Dahle, U.R., Wester, A.L., 2016. Carriage of ESBL/AmpC-producing or ciprofloxacin non-susceptible *Escherichia coli* and *Klebsiella* spp. in healthy people in Norway. Antimicrob. Resist. Infect. Control 5 (1), 57. https://doi.org/10.1186/s13756-016-0156-x.

van Beek, J., Räisänen, K., Broas, M., Kauranen, J., Kähkölä, A., Laine, J., Mustonen, E., Nurkkala, T., Puhto, T., Sinkkonen, J., Torvinen, S., Vornanen, T., Vuento, R., Jalava, J., Lyytikäinen, O., 2019. Tracing local and regional clusters of carbapenemase-producing *Klebsiella pneumoniae* ST512 with whole genome sequencing, Finland, 2013 to 2018. Euro Surveill. 24 (38) https://doi.org/10.2807/1560-7917.ES.2019.24.38.1800522.

Vuopio-Varkila, J., Suppola, J., Klinger, N., Tarkka, E., Kolho, E., 1997. Increase of the number of vancomycin resistant enterococci (VRE) isolated in Helsinki, Finland. Euro Surveill. 2 (12), 97–98. https://doi.org/10.2807/esm.02.12.00174-en.

WHO, 2015. Global Action Plan on Antimicrobial Resistance. World Health Organization, Geneva , Switzerland.

WHO-ECDC, 2022. WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial Resistance Surveillance in Europe 2022 – 2020 Data. *Copenhagen: WHO Regional Office for Europe*. https://www.ecdc.europa.eu/sites/default/files/documents/Joint-WHO-ECDC-AMR-report-2022.pdf.

WHO integrated global surveillance on ESBL-producing E. coli using a "One Health" approach: implementation and opportunities, 2021. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO.

Zykov, I.N., Sundsfjord, A., Småbrekke, L., Samuelsen, Ø., 2016. The antimicrobial activity of mecillinam, nitrofurantoin, temocillin and fosfomycin and comparative analysis of resistance patterns in a nationwide collection of ESBL-producing *Escherichia coli* in Norway 2010–2011. Infect. Dis. 48 (2), 99–107. https://doi.org/10.3109/23744235.2015.1087648.

Swidish Strategy. (n.d.). Swedish Ministry of Health and Social Affairs. Swedish Strategy to Combat Antibiotic Resistance 2020–2023. Retrieved June 21, 2023, from https://www.government.se/499178/globalassets/government/dokument/socialdepartementet/amr_strategi_eng_web.pdf.